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SARCOIDOSIS INVOLVING THE HEART

Report of Case with Sudden Death

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SARCOIDOSIS is not an uncommon disease, but death caused by it per se is infrequent. As indicated by one of the names attributed to it, "lymphogranulomatosis benigna" (Schaumann), the condition is generally benign. However, there are those who feel that this feature is overemphasized inasmuch as death of frank tuberculosis is frequently observed in patients with sarcoidosis. In patients with uncomplicated sarcoidosis there is a tendency of the lesions to regress spontaneously and constitutional symptoms are seldom produced. This is rather surprising in view of the widespread involvement of organs. When death is related directly to sarcoidosis, it occurs because the disease has interfered with the function of such vital structures as the lungs and the heart. Extensive pulmonary sarcoidosis may lead to severe respiratory embarrassment or may cause cor pulmonale (dilatation) and subsequent heart failure. Infiltration of the heart itself may produce cardiac decompensation. It is the latter feature which interests us and is the basis for this report. Recorded cases in which sarcoidosis of the heart was demonstrated at autopsy are few, and sudden death due to this condition has been noted twice in the English literature.[1] The case we present is another instance of sudden death from sarcoidosis.

REPORT OF CASE

A 26 year old Negro employed in a local chair factory, doing light manual labor, ate his usual breakfast and went to work with no complaint. Just before starting work he was sitting on a stool, singing and joking with his fellow workmen. He suddenly fell off the stool and was not seen to move thereafter. His foreman said that he could not feel the pulse of the patient, who appeared to have stopped breathing. On his arrival the ambulance surgeon found the man dead. Information obtained from the wife revealed that about eighteen months prior to the patient's death he complained of "pain around the heart." This was relieved by medicine prescribed by his physician, and there were no further pains. He was

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1. (*a*) Longcope, W. T., and Fisher, A. M.: J. Mt. Sinai Hosp. **8**:784, 1942. (*b*) Bates, G. S., and Walsh, J. M.: Ann. Int. Med. **29**:306, 1948.

rejected by the recruiting staff of the Army on two occasions: the first time because of "poor vision," and the second time for dependency He is said to have had no disability except the "poor vision."

Autopsy (three hours after death).—The body was that of a well developed, well nourished, 26 year old Negro man. Rigor mortis and lividity were absent. No external lesion was observed. The lymph nodes were not palpable.

In the thorax, the thymus was not prominent. The pericardial sac contained about 10 cc. of clear amber fluid, and its surfaces were smooth and glistening. The pleurae were moist and smooth. There were no adhesions or fluid in the pleural cavities. The tracheobronchial lymph nodes were enlarged, measuring from 1 by 1 by 0.5 cm. to 4 by 3 by 2.5 cm. They were held together by dense fibrous tissue, but each could easily be separated from the others. On section they were grayish red or pink and of a rubbery consistency. No area of caseation or hemorrhage was observed. The nodes did not constrict any portion of the tracheobronchial tree. Nor did they infiltrate the lungs or the esophagus, although they adhered to the adjacent pleura, from which they could be readily freed. There were many similar lymph nodes next to the aorta within its arch.

The heart weighed 340 Gm. The myocardium was dark, reddish brown and firm. The right ventricle measured 0.4 cm., the left up to 1.6 cm., in thickness. The endocardium of the left atrium and the left ventricle was slightly thickened and hyalinized. The papillary muscles of the left ventricle were thick and on section presented a pale brown, homogeneous, glistening appearance. The chordae tendineae and the valves were not ususual. The circumferences of the valves were: tricuspid, 12 cm.; pulmonary, 7 cm.; mitral, 11 cm., and aortic, 7 cm. The coronary arteries showed a few small atheromatous plaques along the intima. The orifices were of normal size. The thoracic aorta disclosed a few atheromatous plaques of the intima; no evidence of syphilis was detected.

The left lung weighed 550 Gm.; the right, 650 Gm. All lobes were expanded and crepitant. The periphery of each lobe was pale and emphysematous. On section the lungs were dark grayish red. No pneumonia or edema was detected. The bronchi and the pulmonary vessels were not unusual.

The peritoneal cavity was free of fluid. The serosal surfaces were moist and smooth. The positions of the viscera were not abnormal.

The spleen weighed 225 Gm. It was firm and dark purplish red. The follicles were not clearly delineated.

The liver weighed 1,400 Gm. Its edges were sharp. The parenchyma was firm, and on section the cut surfaces were dark reddish brown. No gross lesions were observed. The gallbladder and the bile ducts were normal.

The gastrointestinal tract revealed congestion of the mucosa, especially in the stomach, and the submucosal lymph follicles of the large intestine were prominent. No other changes were observed. The pancreas was normal.

The mesenteric and paraortic lymph nodes were not remarkable. They were discrete, slightly enlarged and grayish pink on section.

The left kidney weighed 135 Gm.; the right, 150 Gm. The capsules stripped off easily, disclosing smooth red external surfaces. On section the cortices measured up to 0.7 cm. in thickness and were well delineated from the medullae. The latter were congested. The pelves, the ureters and the bladder were normal. The prostate gland and the seminal vesicles appeared normal. The testes were not examined.

The adrenal glands, the abdominal aorta, sections of lumbar vertebrae, the skull and the brain showed no lesions.

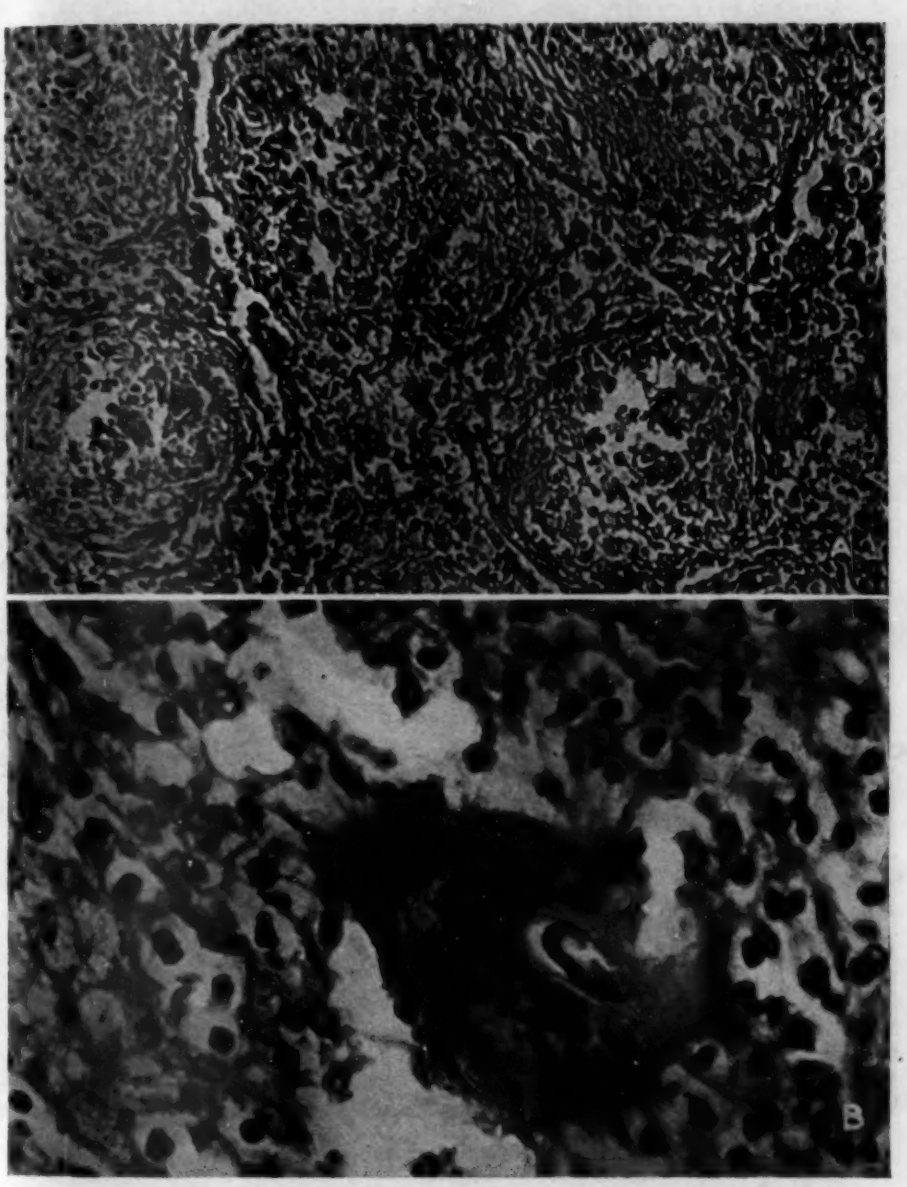

Fig. 1.—*A*, section of a lymph node showing numerous, closely grouped granulomatous (sarcoid) nodules without caseation. Some of the lesions have a fibrillar background. Some hyalinization is present. Hematoxylin and eosin; × 100.

B, sarcoid nodule of a lymph node showing a "Schaumann body" in the cytoplasm of a giant cell. Hematoxylin and eosin; × 500.

Microscopic Examination.—Lymph Nodes: Changes were seen in the tracheobronchial and mesenteric nodes. They were more prominent in the former. Many sections showed practically the entire structure replaced by numerous closely grouped, varying-sized, round or oval nodules composed chiefly of epithelioid cells with few, many or no lymphocytes. In many instances there were a few, irregular,

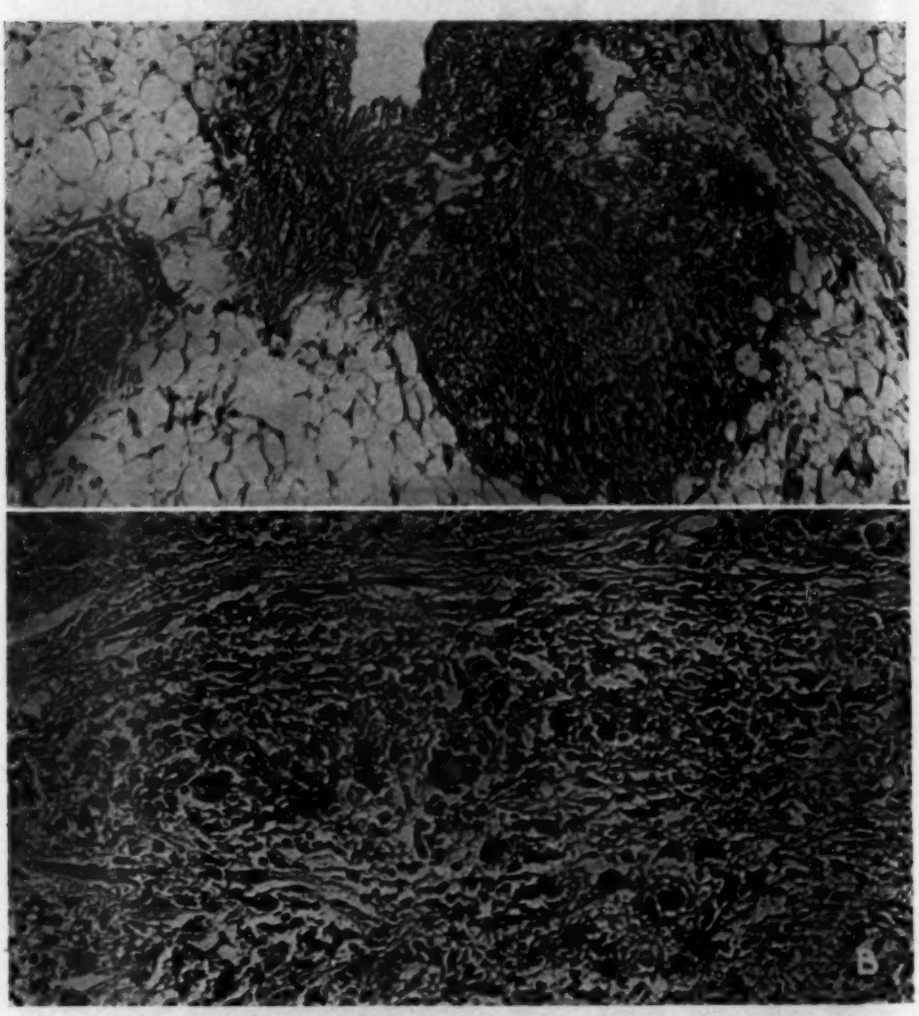

Fig. 2.—*A*, sarcoid lesion in epicardial fat adjacent to a coronary artery. Hematoxylin and eosin; × 75.

B, multiple sarcoid lesions in the myocardium of the left ventricle associated with some fibrosis. Hematoxylin and eosin; × 100.

multinucleated giant cells with abundant, finely granular cytoplasm and many dark-staining nuclei (8 to 40). The latter were located peripherally in some and centrally in others. Several of the giant cells contained basophilic cytoplasmic inclusion bodies made up of distorted concentric lamellas. Occasionally one of the

bodies was observed outside a giant cell. Also occasionally the cytoplasmic inclusion was an irregular, refractile, pale greenish blue, crystal-like structure. No asteroid bodies were identified. The nodules frequently had a background of argentophilic fibrils. Many nodules were completely surrounded by a thick ring of dense, hyalinized tissue which in places extended into and partially or completely replaced the lesions and in certain areas spread over large portions of the lymph node. At times concentric hyalinized rings were seen in the periphery of a lesion or about an arteriole. The hyalinized areas did not give typical reactions for amyloid with congo red and crystal violet stains, but portions stained light pink with congo red. The hyalinized tissue appeared dark green with Masson's trichrome stain for connective tissue and dark blue with Mallory's aniline blue. A striking feature of the lesions was the absence of caseation although the cytoplasm of some of the

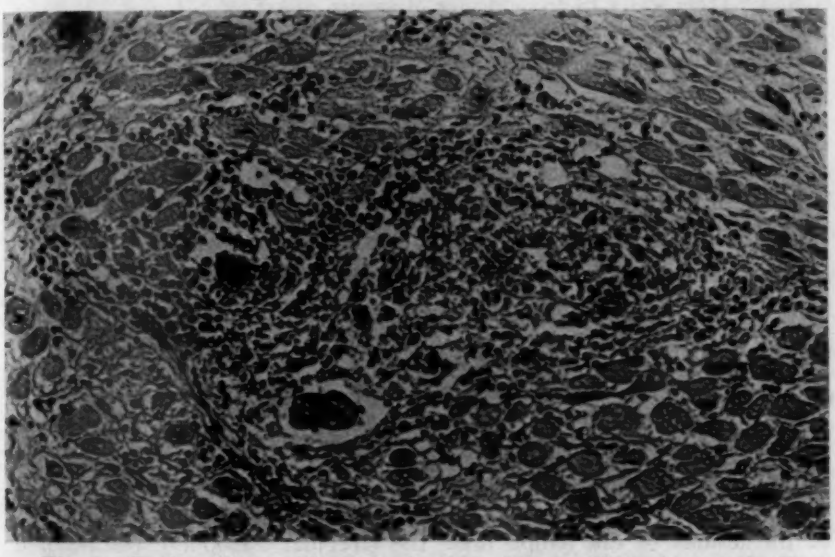

Fig. 3.—Section of a papillary muscle of the left ventricle with muscle fibers replaced to a considerable extent by the collagen associated with sarcoid lesions. More extensive fibrous replacement was noted in areas adjacent to this field. Hematoxylin and eosin; × 100.

epithelioid cells was broken up. Acid-fast bacilli were not found in sections stained by the Ziehl-Neelsen technic. Treponema pallidum was not demonstrated by the Levaditi method.

Heart: Nodules composed of epithelioid cells, lymphocytes and occasional giant cells were found in the subepicardial fat. One of these was adjacent to a coronary artery but did not involve the wall. In sections of myocardium of the left atrium, the interventricular septum, the papillary muscles of the left ventricle and the wall of the left ventricle there were multiple granulomatous lesions like those in the subepicardial fat. They were present at all levels, including the subendocardial region. No cytoplasmic inclusion bodies were seen in the giant cells. These lesions were not as round or as ovoid in many instances as those of the lymph nodes but were nevertheless distinct. No caseation was observed in them. Fibrosis of individual lesions and of the myocardium was noted. In the interventricular septum and the left ventricle, especially in the papillary muscles of the latter, the

muscle fibers had been replaced to a considerable extent by abundant, dense, hyalinized tissue which did not give a positive reaction with the amyloid stains. Sometimes small collections of lymphocytes without the other cellular components of the lesions were seen in the myocardium. Treponema pallidum was not found in sections prepared by the Levaditi technic. A section of mitral valve was normal.

Lungs: Multiple distinct lesions like those described in the lymph nodes were seen throughout all sections. They lacked the dense, hyalinized tissue. No inclusion bodies were seen in the giant cells. Some of the nodules were found extending into the walls of arteries but not into the lumens. The rest of the lung tissue showed considerable hyperemia and some emphysema.

Liver: Nodules similar to those in the lungs were present. They were usually in the periphery of the lobules but were occasionally in the midzone regions. There was a moderate degree of passive congestion.

Prostate Gland: Only one section was made, and in it there was a single, tiny nodule composed of epithelioid cells and a few lymphocytes. No giant cells were noted.

Sections of other organs (aorta, trachea, esophagus, stomach, ileum, colon, spleen, pancreas, adrenal glands, kidneys, urinary bladder, thyroid gland, pituitary gland, brain and bone marrow) disclosed no granulomatous lesions. Except for the prominence of the lymphoid tissue of the stomach, the ileum and the colon, no significant changes were seen.

COMMENT

At autopsy the only remarkable finding was the pronounced thoracic and slight mesenteric lymphadenopathy, which at the time was thought to be consistent with Hodgkin's disease. The cause of the sudden death was not determined until the sections were studied microscopically. The granulomatous lesions noted in the lymph nodes, the heart, the lungs, the liver and the prostate gland were typical of sarcoidosis. Besides the characteristic cellular structure we observed in the giant cells of the lesions of the lymph node the irregular basophilic cytoplasmic inclusion bodies which were described by Schaumann [2] as occurring frequently in the disease. At times the inclusions were refractile and crystal-like. Asteroid bodies, which are sometimes described in sarcoidosis and which were discussed and studied histochemically by Friedman,[3] were not found in our case. These stellate inclusions were first described by Wolbach,[4] in 1911, as associated with disseminated granulomatous lesions which suggest what we now call sarcoid lesions. In the sections of lymph nodes and myocardium (that of the interventricular septum, the left ventricle and especially the papillary muscles of the latter) the extensive hyalinization accompanying the lesions, for the most part, represented collagen, the deposition of which resulted from the healing of the disease. In the sections stained with hematoxylin and eosin some

2. Schaumann, J.: Acta med. Scandinav. **106**:239, 1941.
3. Friedman, M.: Am. J. Path. **20**:621, 1944.
4. Wolbach, S. B.: J. M. Research **24**:243, 1911.

portions of the hyalinized areas, particularly the concentric hyaline rings of the lymph nodes, suggest the "hyalinosis" (paramyloidosis) considered by Teilum [5] as a definite phase of the development of Boeck's sarcoid, with an allergic hyperglobulinosis of the reticuloendothelial system as the underlying primary cause. In the lymph node and heart sections which we studied, the reactions to crystal violet and congo red stains were not typical for amyloid. Only a few small areas of the lymph node stained light pink with congo red.

Careful dissection of the coronary arteries disclosed no obstructive lesions either at the orifices or along the course of the vessels to account for the myocardial fibrosis. One of the granulomatous nodules was found adjacent to a branch of the coronary artery, but it did not compress the vessel. Many sections were made to determine whether there was any obstruction of the arteries elsewhere due to sarcoid nodules, but none was detected. There was no evidence in the gross or the histologic material to indicate rheumatic fever or syphilis as a cause of the fibrosis, unless it is shown by further study that sarcoidosis is a manifestation of the latter disease as some authors [6] contend it is in certain instances.

The sudden death is attributed to the active lesions extensively involving the myocardium, along with the prominent fibrosis. As to the mechanism of the sudden cardiac failure, we cannot say what it was. The possibilities are ventricular fibrillation or depression of the pacemaker or of the auriculoventricular conduction. As to the history of "poor vision," it suggests that the uveal tract may have been involved, as it not uncommonly is in sarcoidosis. The eyes, however, were not sectioned.

Another case of sudden death due to sarcoidosis is noted in a report in which Longcope and Fisher [1a] recorded cases of sarcoidosis involving the heart. Six of 31 patients with sarcoidosis presented evidence during life of some derangement of heart action or showed at autopsy sarcoid lesions of the heart. Cardiac lesions were observed in 3 cases in which autopsies were made. One autopsy, made on a 40 year old Negro man, who supposedly was in good health and who dropped dead on his doorstep, disclosed large masses about the great vessels of the thorax with extensive infiltration of the pericardium and the myocardium. There was enlargement of the superficial, mediastinal, mesenteric and retroperitoneal lymph nodes. Microscopically, the condition proved to be sarcoidosis involving also the lungs, the liver, the kidneys, the spermatic cord, the cerebral dura and the skin of the penis. Another autopsy,

5. Teilum, G.: Am. J. Path. **24**:389, 1948.

6. (*a*) Bernstein, M.; Konzelmann, F. W., and Sidlick, D. M.: Arch. Int. Med. **44**:721, 1929. (*b*) Frazier, C. N., and Hu, C. K.: Proc. Soc. Exper. Biol. & Med. **30**:898, 1933.

on a 42 year old Negro man who had cardiac symptoms during life and who became mentally deranged and committed suicide, showed fresh and old sarcoid lesions present throughout the myocardium and the pericardium. Lesions were noted also in the pleura, the lungs, the spleen, the liver and the kidneys. There was, in addition, a dense scar in the interventricular septum. No evidence of syphilis was detected, but the authors could not exclude syphilis as a cause of the scar. In a third autopsy, on a patient who had no cardiac symptoms during life, a few lesions were found in the myocardium.

Recently Bates and Walsh [1b] described a case of sudden death due to sarcoidosis in a report dealing with observations on 7 patients with Boeck's sarcoid. One of these, a 31 year old Negro man, complained of anorexia, weakness, and pain in the calves for two months, and a diagnosis of pseudohypertrophic muscular dystrophy was made. Later, however, the presence of sarcoidosis was established by examination of a surgically removed epitrochlear lymph node. Ten months after the onset of symptoms there was "sudden and unexpected death." At autopsy sarcoid lesions were found throughout the myocardium (both ventricles, the interventricular septum and the papillary muscles) associated with fibrosis. Lesions were also noted in the epicardium, the lungs, the liver, the kidneys, the spleen, the tracheobronchial lymph nodes and the voluntary muscles. Before death there were no symptoms suggesting cardiac involvement, although the authors felt that the persistent tachycardia (90 to 120), even when the patient was afebrile, should have been a warning that the myocardium was invaded by sarcoidosis.

As far as we have been able to determine, the article by Bernstein, Konzelmann and Sidlick [6a] was the first in which there was reported an autopsy of a patient in whom this disease had involved any of the structures of the heart. Their patient was a 52 year old white man with no apparent cardiac complaints. He had multiple lesions of the skin and a chronic respiratory ailment. He had dyspnea due to the respiratory disease and hydrothorax and died of bronchopneumonia. Lesions which were considered by the authors to show the histologic changes of sarcoidosis were found in the skin, the bronchial mucosa and the mucosa of the ileum. Nodules were also present in the epicardium, situated along the coronary vessels. Grossly the superficial muscle fibers were invaded for a distance of 4 or 5 mm., but there was no histologic description of any lesion of the myocardium or the endocardium.

Schaumann [7] gave an account of 4 cases of sarcoidosis in which autopsies were made. One of the patients, a 45 year old white man,

7. Schaumann, J.: Brit. J. Dermat. **48**:399, 1936.

had extensive cutaneous and visceral involvement and died of cardiac failure. The author felt that the "asthenia of the heart, arising both from the increased resistance produced by the lung-lesion and from the localization of the disease in the heart, was presumably the cause of the death, although it seems impossible to gauge what part the advanced destruction of the haematopoietic apparatus played in the fatal issue." At autopsy he found enlargement of the heart, chiefly hypertrophy and dilatation of the right chamber. Histologically, he noted sarcoid lesions in the epicardium, and in the interstices of the myocardium there was "some slight cell infiltrate" but no "epithelioid foci." Besides the cardiac lesions and the extensive involvement of the skin and the lungs, nodules were found in the liver, the spleen, lymph nodes (cervical, axillary, inguinal, tracheal, bronchial, mesenteric, iliac and those in the hilus of the spleen and the liver), the capsules of the kidneys, the bone marrow, the tendon sheaths (hand) and the tonsils.

Nickerson [8] reported 6 cases of sarcoidosis in which autopsies were made. In 5 of these there were no outstanding gross findings except the major disease causing death. The most constant feature he found was unexplained splenomegaly with or without abdominal lymphadenopathy. In 1 case there was an acute overwhelming sarcoidosis. The patient, a 58 year old Negro woman, had dyspnea related to the pleural effusion. The heart sounds were regular, rapid and weak. No murmurs were heard. At autopsy there were multiple nodules in the parietal pericardium and a few solitary lesions in the myocardium and subendocardial fibrous tissue. Also involved were the parietal pleura, the lungs, the spleen, the liver, lymph nodes and an eyelid.

Another case of generalized sarcoidosis with autopsy was recorded by Spencer and Warren.[9] The patient was a 51 year old man who had no clinical evidence of cardiac involvement. His death was due to obstruction of the airway following edema of the larynx. Autopsy disclosed sarcoid lesions in the myocardium as well as in the lungs, the skin, the liver, the spleen, lymph nodes (bronchopulmonary, tracheal, paravertebral, iliac and inguinal), the trachea, the thyroid gland and the kidneys.

Extensive involvement of the myocardium with fibrosis and lesions of the endocardium, including nodules on the mitral valve, were disclosed in a case presented by Cotter.[10] The patient, an 18 year old Negro youth, had clinical evidence of cardiac derangement and died of progressive myocardial failure. Autopsy revealed other lesions in

8. Nickerson, D. A.: Arch. Path. **24**:19, 1937.
9. Spencer, J., and Warren, S.: Arch. Int. Med. **62**:285, 1938.
10. Cotter, E. F.: Arch. Int. Med. **64**:286, 1939.

the lungs, peritracheal and hilar lymph nodes, the liver, the spleen, a testicle, the wall of the alimentary tract, subcutaneous tissue and underlying muscle.

A review of the literature dealing with sarcoidosis of the heart was published by Johnson and Jason [11] in 1944. These authors also reported a case of their own. The patient, a 24 year old Negro man, had symptoms referable to the cardiac lesions which caused his death. They found massive infiltration of the myocardium, not unlike that in Cotter's case, together with lesions of the epicardium, the endocardium, the visceral pleura, the lungs, the spleen, the liver, thoracic and upper abdominal lymph nodes and the testes. Johnson and Jason stated that "a review of the case reports of Boeck's sarcoid with cardiac lesions is hampered by the lack of uniformity in diagnostic criteria and the fact that many authors are of the opinion that sarcoidosis is a proliferative and non-caseating form of tuberculosis." As they pointed out, conditions have been reported as "atypical tuberculosis," "specific myocarditis," "granulomatous myocarditis" or "myocarditis of unknown cause" which may represent sarcoidosis of the heart. One report, among others, to which they refer is that of Brosig's concerning a patient who died suddenly. According to these authors, the lesions in that case which extensively involved the mediastinal nodes and the heart cannot be distinguished microscopically from sarcoidosis.

In a case of coexistent pulmonary asbestosis and sarcoidosis discussed by Skavlem and Ritterhoff,[12] sarcoid lesions were found incidentally in the myocardium of the right and left ventricles. Those in the right ventricular myocardium were accompanied by considerable fibrosis. The patient was a 42 year old white man who worked in an asbestos plant for twenty-five years. He had no cardiac symptoms at any time. Dyspnea was related to the lung disease. Autopsy disclosed, in addition to the pulmonary and myocardial involvement, sarcoid nodules of the tracheobronchial lymph nodes, the spleen, the liver, the kidneys and the diaphragm. Interestingly, the authors found both types of characteristic inclusions in the lesions, "Schaumann bodies" and asteroid bodies, a combination which they did not observe in other reported cases.

Hauser [13] presented 19 cases of pulmonary sarcoidosis, in 4 of which autopsies were made. One of the patients, a Negro woman aged 27 years, died of respiratory and cardiac failure (cor pulmonale) following a period of progressive dyspnea. Sarcoid lesions were seen in the pericardium but nowhere else in the heart. The following organs were

11. Johnson, J. B., and Jason, R. S.: Am. Heart J. **27**:246, 1944.
12. Skavlem, J. H., and Ritterhoff, R. J.: Am. J. Path. **22**:493, 1946.
13. Hauser, H.: J. Oklahoma M. A. **39**:395, 1946

Sarcoidosis Involving the Heart: 13 Cases in Which Autopsies Were Made

Author and Patient	Clinical Evidence of Cardiac Involvement	Cause of Death	Lesions of Heart	Lesions of Orther Organs
Bernstein and others,[6a] 52 yr. white man	None (dyspnea due to respiratory disease and hydrothorax)	Bronchopneumonia	Epicardium	Skin, bronchial mucosa, intestinal mucosa
Schaumann,[2] 45 yr. white man.....	Congestive heart failure (due to cor pulmonale and possibly to cardiac lesions)	Cardiac failure (due to cor pulmonale and possibly to cardiac lesions)	Epicardium	Lungs, liver, spleen, skin, lymph nodes, tonsils, bone marrow, tendon sheaths (hand), capsule of kidneys
Nickerson,[8] 58 yr. Negro woman...	None (dyspnea due to pleural effusion)	Acute, overwhelming sarcoidosis	Parietal pericardium, myocardium, subendocardial fibrous tissue	Parietal pleura, lungs, liver, lymph nodes, spleen, eyelid
Spencer and Warren,[9] 51 yr. man..	None	Obstruction of airway (edema of larynx)	Myocardium	Lungs, skin, liver, spleen, lymph nodes, kidneys, trachea, thyroid gland
Cotter,[10] 18 yr. Negro man.....	Progressive myocardial failure	Sarcoidosis of heart	Myocardium Endocardium	Lungs, lymph nodes, liver, spleen, alimentary tract, subcutaneous tissue and underlying muscle, testis
Longcope and Fisher,[1a] 40 yr. Negro man	None known	Sarcoidosis of heart—death sudden	Pericardium Myocardium	Lymph nodes, lungs, liver, kidneys, spermatic cord, cerebral dura, skin (penis)
42 yr. Negro man.....	Stokes-Adams syndrome; auriculoventricular dissociation	Suicide	Pericardium Myocardium	Pleura, lungs, spleen, liver, kidneys
*	None	*	Myocardium	*
Johnson and Jason,[11] 24 yr. Negro man	Premature ventricular beats; ventricular tachycardia and severe congestive heart failure	Sarcoidosis of heart	Epicardium Myocardium Endocardium	Visceral pleura, lungs, spleen, lymph nodes, liver, testis
Skaviem and Ritterhoff,[12] 42 yr. white man	None (dyspnea related to lesions of lungs)	Respiratory failure (coexistent asbestosis and sarcoidosis)	Myocardium	Lungs, lymph nodes, spleen, liver, kidneys, diaphragm
Hauser,[13] 27 yr. Negro woman.....	Progressive dyspnea (respiratory and cardiac: cor pulmonale)	Respiratory and cardiac failure (cor pulmonale)	Pericardium	Lungs, bronchi, pleura, spleen, right kidney, lymph nodes
Bates and Walsh,[1b] 31 yr. Negro man	Persistent tachycardia	Sarcoidosis of heart—death sudden	Myocardium Epicardium	Lungs, liver, kidneys, spleen, tracheobronchial lymph nodes, voluntary muscles
Scotti and McKeown: Arch. Path., present issue, 26 yr. Negro man	No accurate history, but apparently no symptoms—said to have had "pain around heart" once	Sarcoidosis of heart—death sudden	Epicardium Myocardium	Lymph nodes, lungs, liver, prostate

* The details were not given in the article.

also involved: lungs, bronchi, pleura, spleen, right kidney and lymph nodes (mediastinal, left inferior deep cervical, pretracheal, celiac, hepatic and paraortic).

In these reported cases of sarcoidosis of the heart noted in the English literature (see accompanying table) only 3 of the 13 patients had cardiac symptoms attributable to the lesions of the heart alone. Another had no symptoms suggesting cardiac involvement, but we felt that the persistent tachycardia, which was present even when the patient was afebrile, should have been a warning that the myocardium was invaded by sarcoidosis. Five patients died as a result of myocardial involvement; 3 of these, 2 of whom were presumably in good health during life, died suddenly. Two died of cardiac failure due to increasing pulmonary resistance (cor pulmonale) caused by extensive infiltration of the lungs, and in one of these, according to the author, weakness of the heart was possibly due also to cardiac localization of the lesions.

SUMMARY

A case of sarcoidosis involving the heart, with sudden death, is presented. There were numerous lesions in the myocardium, associated with considerable fibrosis. Lesions were also present in the epicardium, in thoracic and mesenteric lymph nodes and in the lungs, the liver and the prostate gland.

Twelve cases of sarcoidosis of the heart reported by other authors, in which autopsies were made, are briefly reviewed. Among these were 2 cases with sudden death.

CHRONIC INFLAMMATORY LESIONS OF SKELETAL MUSCLE IN RHEUMATOID ARTHRITIS AND IN OTHER DISEASES

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DESPITE the fact that voluntary muscle normally constitutes about 50 per cent of the body mass, pathologic studies of this tissue are infrequently reported. This is remarkable when one considers the profound changes which occur in the skeletal muscles in many of the more chronic systemic diseases. New interest has been stimulated in this subject by recent reports of inflammatory lesions occurring in skeletal muscle in patients with rheumatoid arthritis.

While the outstanding feature of rheumatoid arthritis is the involvement of the joints, the rapid wasting and the extreme degree of atrophy of muscles which accompany the more severe forms of the disease are of considerable interest. The latter feature is not necessarily limited to those muscles directly associated with the involved joints, but often is more generalized. Moreover, it is usually of greater severity than can be accounted for on the basis of spasm, disuse or emaciation of muscles.

Indicative of the systemic nature of the disease, Curtis and Pollard,[1] in 1940, first reported on the perivascular infiltrations of inflammatory cells occurring in skin and muscle of patients with rheumatoid arthritis. The cells were chiefly lymphocytes and were found in the skeletal muscles of 5 of 11 patients from whom specimens of muscles were taken for biopsies. This included 2 of 3 patients whose symptoms conformed to the criteria of the so-called Felty's syndrome. No conclusion was drawn other than that the lesions probably indicated the presence of some generalized infectious process.

In 1945 Freund and associates [2] noted small inflammatory nodules in the muscles of amputated lower limbs from a patient with rheumatoid arthritis and substantiated this finding by consistently demonstrating lesions in biopsy specimens from 14 patients who had typical rheumatoid arthritis. This work was extended by Steiner and co-workers,[3a] who

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1. Curtis, A. C., and Pollard, H. M.: Ann. Int. Med. **13**:2265, 1940.

2. Freund, H. A.; Steiner, G.; Leichtentritt, B., and Price, A. E.: Science **101**:202, 1945.

3. Steiner, G.; Freund, H. A.; Leichtentritt, B., and Maun M. E.: (*a*) Am. J. Path. **22**:103, 1946; (*b*) footnote, p. 120.

described the same lesions in all of 9 patients with rheumatoid arthritis, one of whom was encountered in a series of 196 controls. Small lymphocytic infiltrations were found in only one other person, a patient with subacute bacterial endocarditis superimposed on old rheumatic heart disease. The remainder of the controls showed no such lesions. Subsequent examination of 5 additional patients with rheumatoid arthritis showed identical lesions.[3b]

The lesions consisted of nodular and focal collections of lymphocytes and plasma cells, together with occasional mast cells, polymorphonuclear leukocytes and eosinophils. In some of the larger nodules epithelioid cells were noted. There was no evidence of necrosis. The nodules were found chiefly in the perimysium separating muscle bundles and in the endomysium infiltrating between the individual muscle fibers. Lesions of the epimysium were uncommon. Some of the focal collections occurred around and in close relation to small blood vessels, and actual infiltration of the vessel walls was described. Associated degenerative change of the muscle fibers was the rule.

These authors regarded the lesions as specific and essential findings in rheumatoid arthritis, and they considered the associated muscle degeneration as a consequence of the inflammtory lesion. Their occurrence in muscles in cases of rheumatoid arthritis has been confirmed by subsequent investigations,[4] although they have not been encountered in all cases. The application of this new finding as an aid to diagnosis has been advocated.[5]

OBJECT OF THE PRESENT STUDY

The present study was undertaken in order to determine the specificity or the nonspecificity of the lesions under discussion. Sections of skeletal muscle taken routinely during the past ten years in the departments of pathology, surgical pathology and neuropathology of the Toronto General Hospital were carefully reviewed, as well as additional sections obtained in a group of selected cases. The latter were chosen from among cases of diseases in which pathologic changes of muscle might be expected to occur. In all a total of 158 cases were examined. Sections were routinely stained with hematoxylin and eosin.

RHEUMATOID ARTHRITIS

Fifteen cases of chronic rheumatoid arthritis which came to autopsy were reviewed. All were cases of long standing, the disease having been present for one

4. (*a*) Gibson, H. J.; Kersley, G. D., and Desmarais, M. H. L.: Ann. Rheum. Dis. **5**:131, 1946. (*b*) Clawson, B. J.: Am. J. Path. **22**:647, 1946. (*c*) de Forest, G. K.; Bunting, H., and Kenney, W. E.: Am. J. Med. **2**:40, 1947.

5. Steiner and others.[3] de Forest and others.[4c]

and a half to fifty-five years. In two thirds of the cases the history was in excess of five years' duration. The ages of the patients varied from 14 to 76 years at the time of death; all but 1 were over 40 years of age.

Sections were cut from stock material, the tissue customarily being taken from the rectus abdominis muscle. Cellular accumulations or infiltrations probably indicative of inflammatory lesions were found in 3 of the 15 cases. In the sections from 2 of these 3 cases there were small nodular or focal collections of cells consisting chiefly of lymphocytes, a few plasma cells and occasional eosinophils and polymorphonuclear leukocytes. The nodular collections were distinctly microscopic in size and were situated in the endomysial (fig. 1) or the perimysial (fig. 2) tissues. The endomysial lesions within the muscle bundles were sometimes associated with evident degenerative changes of one or several muscle fibers (fig. 3). In the perimysial tissue between muscle bundles the lesions were often perivascular or paravascular in location, but infiltration of the vessel walls was not noted. In both cases there was shown a mild to moderate degree of atrophy of muscle, as evidenced by shrinkage and vacuolation of single or at most a few muscle fibers, proliferation of sarcolemma nuclei and fatty replacement. In other areas similar degenerative changes were commonly seen in the muscle fibers without evidence of any inflammatory reaction. In the third case the muscle contained a diffuse type of lesion (fig. 4) accompanied by mild degenerative changes of the muscle.

The sections representing the remaining 12 cases disclosed no lesions of an inflammatory nature despite the fact that degenerative changes were noted in 3 instances. This was of equal or greater severity than in those cases in which inflammatory lesions were demonstrated.

Biopsy material from muscles of limbs was examined in 5 cases of active rheumatoid arthritis varying in duration from one to twenty-six years. Cellular lesions were encountered in 2 cases, consisting largely of small focal collections of lymphocytes. Evidence of atrophy of muscle was present in both. No lesions were found in the 3 remaining cases in spite of moderate to severe degenerative changes in the muscles.

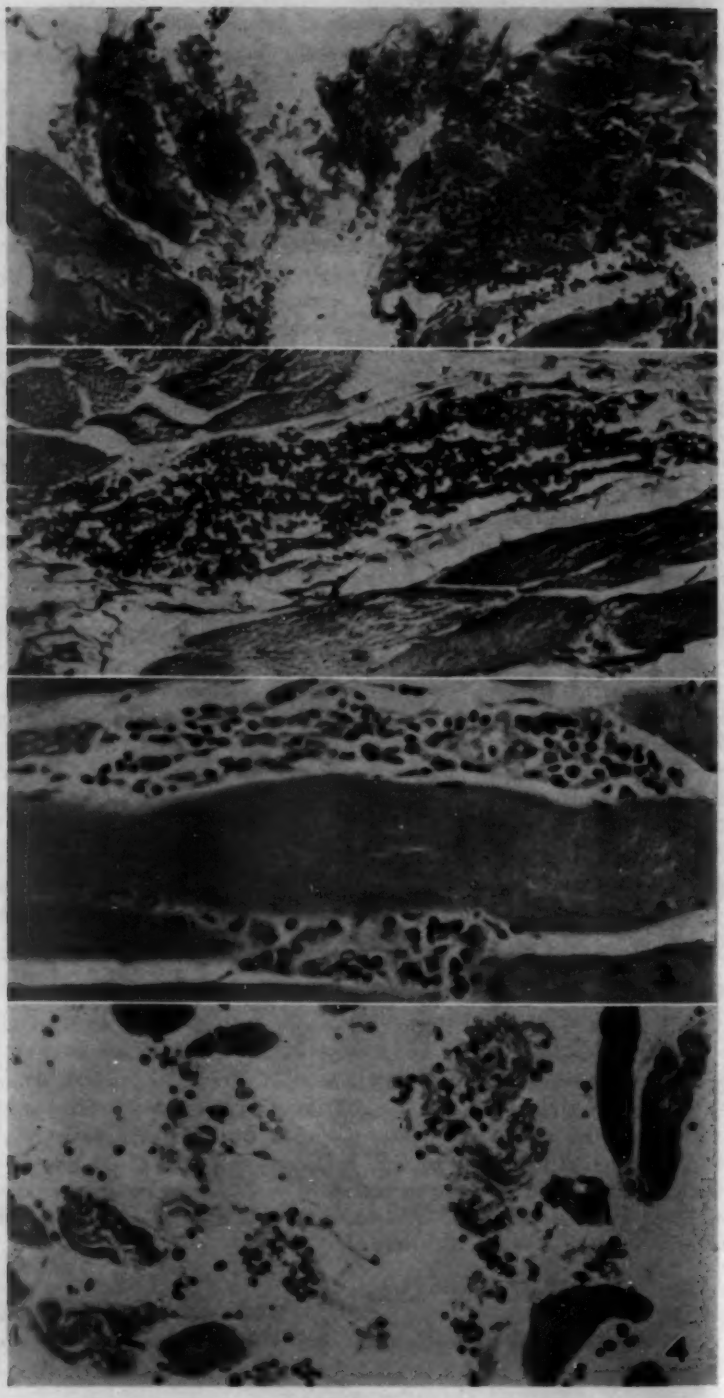
The technic employed in these 20 cases of rheumatoid arthritis was that routinely used in examining surgical material. An average of three sections were cut in each instance. In cases showing no lesions examinations were repeated, additional blocks of muscle being used.

ANKYLOSING (STRÜMPELL–MARIE) SPONDYLITIS

Owing to the difference of opinion which prevails in regard to the nature of this disease, the findings are not included with those of rheumatoid arthritis. Sections of muscle were examined from 6 cases: In 3 of these cases the tissue had been obtained for biopsy, and in 3 it was from autopsy material. The duration of illness varied from four to nine years. Degenerative changes of moderate degree were present in 3 of the cases, but focal inflammatory lesions of the type described in the foregoing section were not encountered. In 1 instance there were occasional lymphocytes and plasma cells about one or two small arterioles, but these were not impressive and might readily be overlooked.

OTHER TYPES OF ARTHRITIS

Biopsy material from 2 cases of gonorrheal arthritis revealed no inflammatory lesions, although a mild degree of muscle atrophy was present.



Figures 1-4

Sections were obtained for biopsy from 2 patients with gout. In one instance the tissue revealed nothing. In the other the specimen, removed from an area adjacent to tophaceous deposits, contained diffuse and focal lymphocytic infiltrations. A third patient was clinically suspected to have gout, but the history was not characteristic and no tophaceous lesions were demonstrated at autopsy to support the diagnosis; yet distinct periarteritis was revealed microscopically. The lesions of muscle consisted of perivascular infiltrations of lymphocytes and plasma cells (fig. 5), the cells often infiltrating the vessel walls. The affected arterioles were considerably thickened and the lumens narrowed. Cellular proliferation within the walls of the vessels was a prominent feature, with areas of fibrinoid change. The patient was a 57 year old man with a history of recurrent arthritis of multiple joints of eight years' duration. Treatment with cinchophen had been started one year before death but was discontinued after three months because of a complicating hepatitis. The immediate cause of death was bronchopneumonia with congestive heart failure. Viscera showed lesions similar to those found in muscle but of a milder degree.

Small focal and perivascular collections of lymphocytes were encountered in muscle from a 48 year old woman with a twelve months' history of nonspecific arthritis involving the small joints of the hands. Death was due to cerebral hemorrhage. The history had not been obtained in sufficient detail to include this case as one of rheumatoid arthritis, and the joints had not been examined at autopsy. Microscopically, there was no evidence of muscle degeneration.

Diffuse focal and perivascular lesions were also found in muscle from a 45 year old woman with a five months' history of acute polyarthritis. Death was attributed to sulfonamide intoxication. The inflammatory lesions consisted of lymphocytes, plasma cells, a high proportion of large, pale mononuclear cells and occasional polymorphonuclear leukocytes.

DERMATOMYOSITIS

Biopsies made in 4 cases of dermatomyositis, in each of which the clinical picture was characteristic, all demonstrated well marked inflammatory lesions. The most prominent were focal collections of lymphocytes, plasma cells, occasional large mononuclear cells and, rarely, a few polymorphonuclear leukocytes (fig. 6). In some areas there was extension of the infiltrations between individual muscle fibers, while in 2 cases a diffuse infiltration of cells also was present. Perivascular collections were commonly encountered both within and between the muscle bundles. In 2 cases degenerative changes in the muscle fibers were mild; in the others they were of a modrate degree.

DISSEMINATED LUPUS ERYTHEMATOSUS

Sections of muscle were examined from 4 patients with disseminated lupus erythematosus who came to autopsy. No inflammatory lesions were noted in the muscle of 1 patient, while that of the remaining patients contained obvious lesions.

Fig. 1.—Focal chronic inflammatory lesions of the endomysial tissue of skeletal muscle in a case of rheumatoid arthritis. Two small vessels are present in the upper left hand corner. × 160.

Fig. 2.—A focal or nodular collection of chronic inflammatory cells in the perimysial tissue between muscle bundles in a case of rheumatoid arthritis. The muscle is well preserved. × 250.

Fig. 3.—Small endomysial collections of cells in a case of rheumatoid arthritis. × 300.

Fig. 4.—Diffuse infiltration of muscle in a case of rheumatoid arthritis. There is considerable edema of the tissue with wide separation of the fibers. × 250.

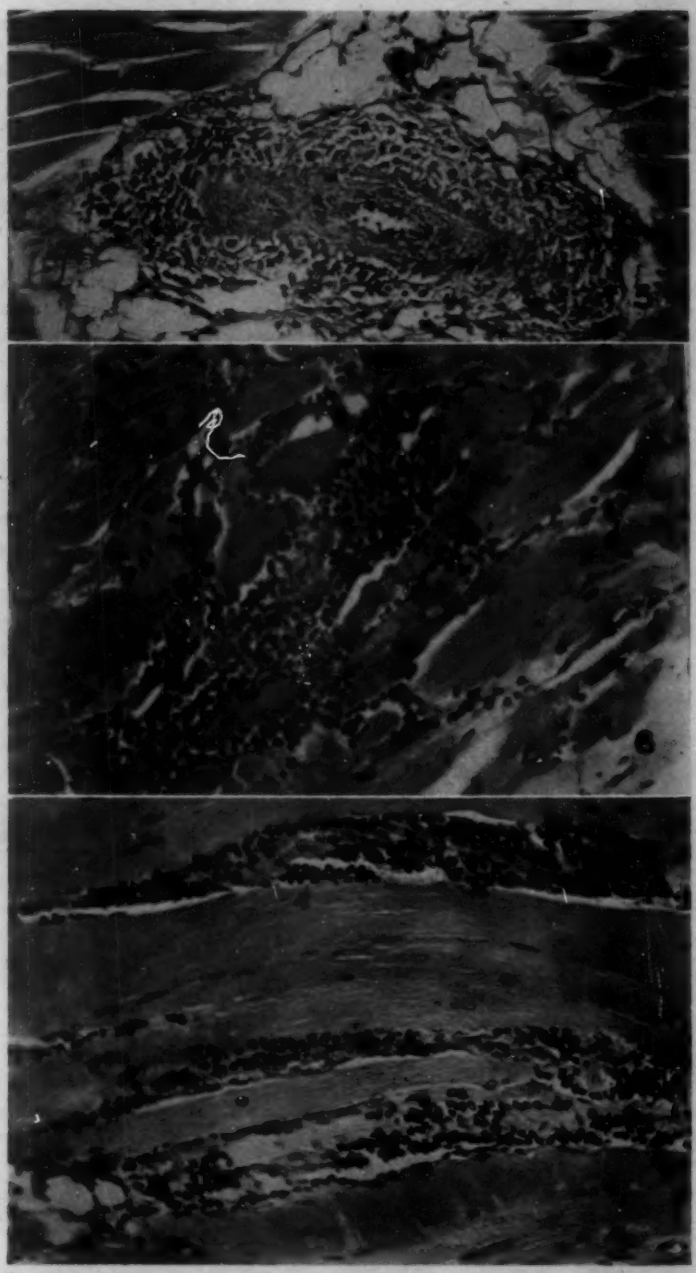


Fig. 5.—A section of muscle from a patient with questionable gout who had been treated with cinchophen nine months previously. Distinct periarteritis is present. × 160.

Fig. 6.—A nodular collection of chronic inflammatory cells in the endomysial tissue of muscle from a patient with dermatomyositis. × 250.

Fig. 7.—Focal collections of chronic inflammatory cells in muscle in a case of disseminated lupus erythematosus. × 225.

These included focal (fig. 7) and perivascular collections of cells, with occasional diffuse infiltrations between individual muscle fibers. The cells comprised chiefly lymphocytes, occasional plasma cells and a few polymorphonuclear leukocytes or eosinophils. Degeneration of muscle fiber was mild in 2 cases and not evident in the others.

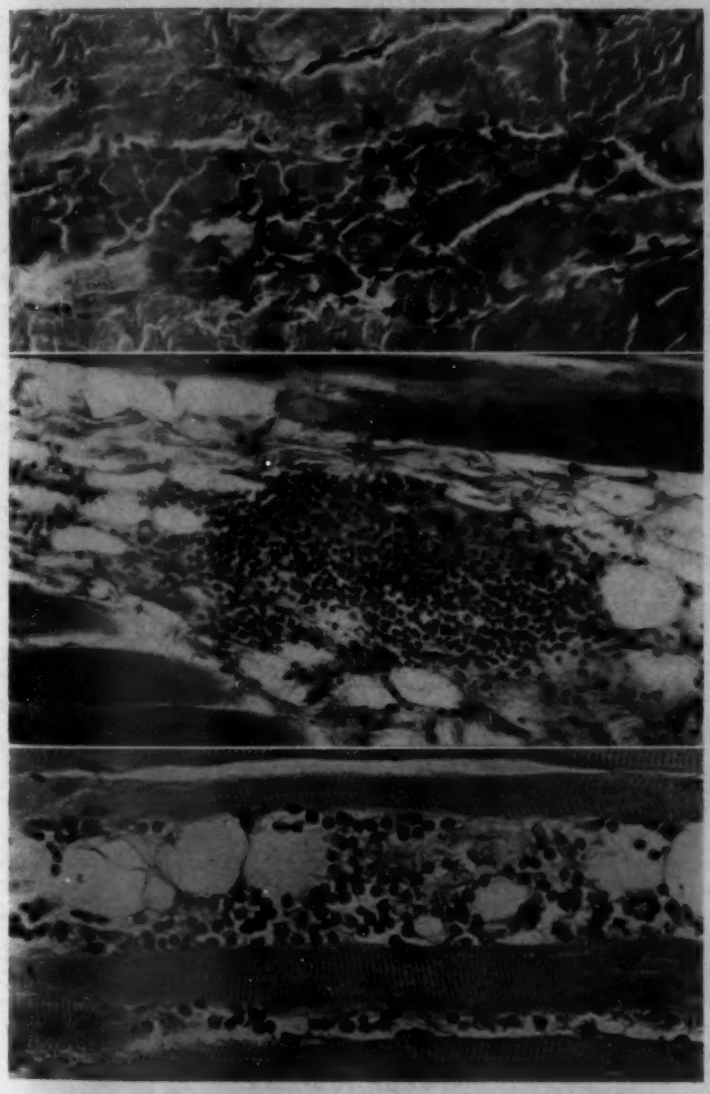


Fig. 8.—An endomysial collection of chronic inflammatory cells, not related to any vessel, in a case of periarteritis nodosa. × 250.

Fig. 9.—A nodular lesion of perimysium in a case of Addison's disease. × 225.

Fig. 10.—A small endomysial lesion in a case of hyperthyroidism. × 300.

PERIARTERITIS NODOSA

In sections of muscle obtained from 2 patients with periarteritis nodosa, from one at biopsy and from the other at autopsy, the arterial and periarterial lesions—comparable to those illustrated in fig. 5—were the prominent feature, though small focal collections of cells were present also in the endomysium. The cells were mainly lymphocytes, odd plasma cells and a few large mononuclear cells. The specimen obtained at biopsy contained a large proportion of eosinophils. In 1 other case examined post mortem, small focal collections were the only lesions present (fig. 8); the typical periarteritis was not evident in the muscle sections.

ADDISON'S DISEASE

In 7 cases of Addison's disease muscles were examined at autopsy. In 3 of these the sections contained lesions. In 1 case there were large focal (fig. 9) and small perivascular collections of lymphocytes and plasma cells, with a few large mononuclear cells. In 2 others minute collections of lymphocytes, numbering about 15 to 20 cells, were noted, usually in relation to single degenerating muscle fibers. No lesions were observed in the remainder of the cases, though moderately severe atrophy of muscle was evident in 1.

HYPERTHYROIDISM

In 2 of 3 cases of hyperthyroidism that came to autopsy the muscles contained lesions. In one instance the lesions were focal (fig. 10), and in the other the lesion was diffuse, with considerable atrophy and edema of muscle. The cells were predominantly lymphocytes; a few plasma cells and occasional polymorphonuclear leukocytes or large mononuclear cells were seen. One section of extraocular muscle in a case of malignant exophthalmos showed considerable edema, atrophy and diffuse lymphocytic infiltration.

MYXEDEMA

In 4 cases of myxedema sections disclosed no inflammatory lesions. In 1 case multiple clusters of small round or oval cells with darkly staining nuclei were observed. These appeared to be located within the sheaths of the individual muscle fibers and resembled sarcolemma cells (fig. 11).

SUBACUTE BACTERIAL ENDOCARDITIS

Lesions of muscles were found in only 2 of 6 cases of subacute bacterial endocarditis examined post mortem. In one the lesions consisted of tiny focal collections of lymphocytes, plasma cells and occasional polymorphonuclear leukocytes, usually in relation to single degenerating muscle fibers. In the other the involved muscle contained large focal collections (fig. 12) of lymphocytes and plasma cells and, in addition, a high proportion of polymorphonuclear leukocytes and large, pale mononuclear cells. The muscle fibers showed moderately severe degenerative changes without necrosis.

RHEUMATIC FEVER

No inflammatory lesions of muscle were encountered in 5 cases of rheumatic disease of the heart with microscopic evidence of active myocarditis. In 1 case the history was of four months' duration, and there was an acute and severe reaction in the heart muscle.

MYASTHENIA GRAVIS

Biopsy material was obtained from 10 patients said to be suffering from myasthenia gravis. In 2 cases the sections of muscle revealed small focal lymphocytic collections (fig. 13). Muscle degeneration and atrophy were present in all instances, and in some were severe. The diagnosis of myasthenia gravis was not verified in all instances, however. Six of the patients were not hospitalized, and their diagnosis must remain in doubt.

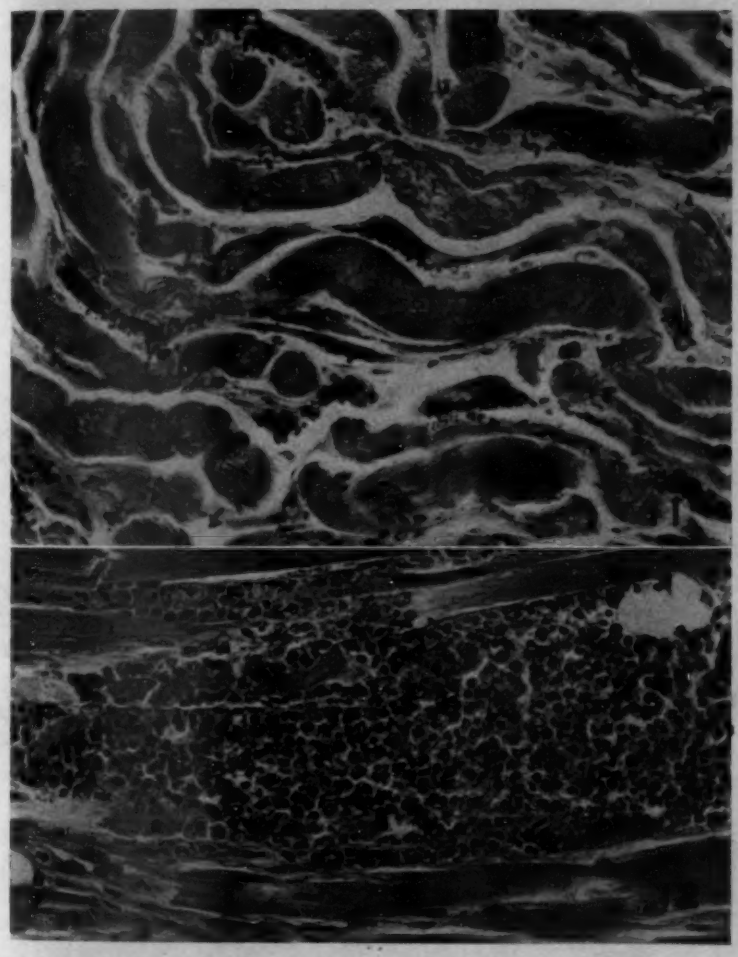


Fig. 11.—Dense proliferations of sarcolemma cells in skeletal muscle in a case of myxedema. The clusters of cells occur in relation to degenerating fibers. × 230.

Fig. 12.—A large nodular lesion of endomysium in a case of subacute bacterial endocarditis. Many large mononuclear cells and polymorphonuclear leukocytes are present, as well as lymphocytes and plasma cells. × 250.

MUSCULAR ATROPHY AND MUSCULAR DYSTROPHY

Included in this group are 4 cases of amyotrophic lateral sclerosis, 3 cases of muscular dystrophy and 1 case each of progressive muscular atrophy, Charcot-

Marie-Tooth disease (progressive neuropathic [peroneal] muscular atrophy), juvenile myopathy and diffuse neuronal degeneration, in all of which moderate to severe muscle degeneration was observed without evidence of inflammatory lesions. In 1 case of fascioscapulohumeral atrophy the muscle contained small, focal collections of lymphocytes with occasional plasma cells (fig. 14).

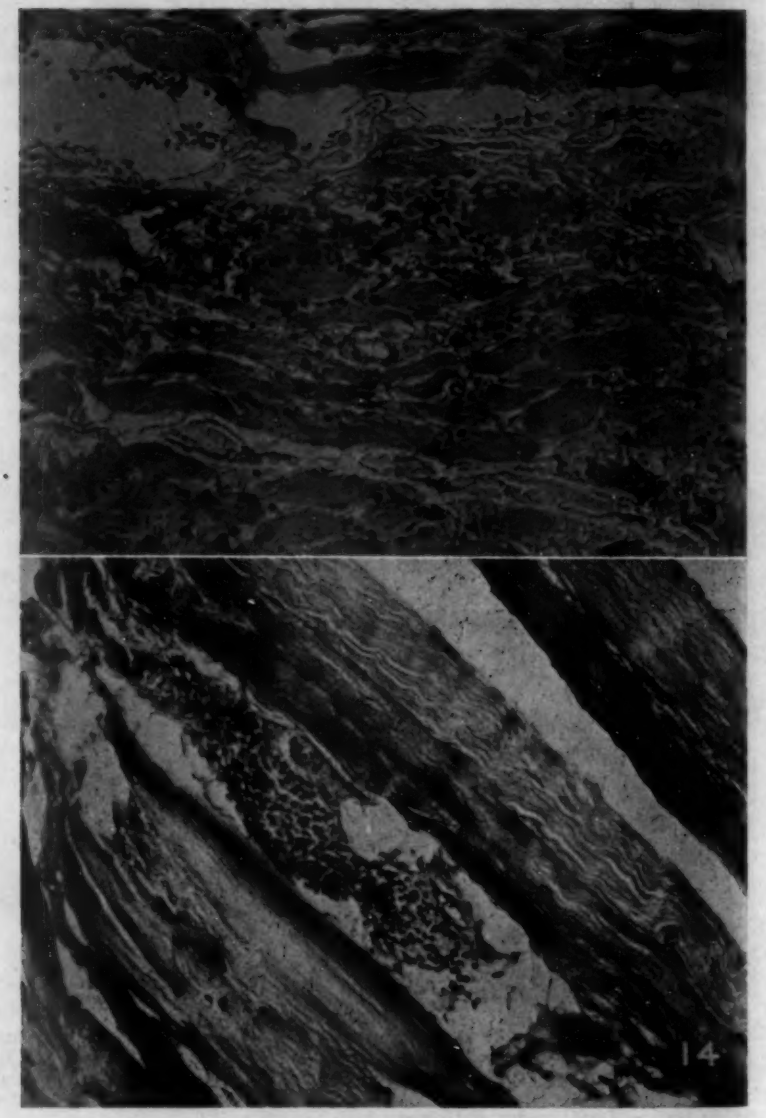


Fig. 13.—A small endomysial lesion in a case of myasthenia gravis. The muscle fibers show severe degenerative changes. × 250.

Fig. 14.—A small focal lesion of muscle in a case of fascioscapulohumeral atrophy. × 250.

MISCELLANEOUS DISEASES OF THE CENTRAL NERVOUS SYSTEM AND PERIPHERAL NERVES

This group includes 4 cases of tabes dorsalis, 5 of subacute combined degeneration, 2 of multiple sclerosis, 5 of poliomyelitis varying in duration from one to forty years, 3 in which sympathectomy had been performed, 3 of peripheral neuritis and 1 of injury of the spinal cord. In 2 cases of subacute combined degeneration muscle sections contained diffuse infiltrations of the perimysial tissue, the participating cells being lymphocytes, plasma cells, polymorphonuclear leukocytes and a few, large pale mononuclear cells. Degenerative muscle changes varied from none to severe in this group. In 1 case of peripheral neuritis a section of muscle contained a large focal collection of lymphocytes, with a few large mononuclear and occasional plasma cells. This was located in the perimysial tissue.

MISCELLANEOUS CONDITIONS

Biopsy sections were examined in 43 cases of various conditions. Chronic myositis was present in 1 case of myositis ossificans following trauma, and in 1 case of amputation neuroma. Apart from frank sepsis in 2 cases, no significant lesions were encountered in the remainder.

COMMENT

It is not the purpose in this report to discuss in detail the many lesions which may be encountered in the skeletal muscles in various diseases. An attempt has been made merely to study a variety of sections from routine and selected material with a view to estimating the frequency of occurrence of nonsuppurative chronic inflammatory lesions. Attention was directed in particular to small focal, diffuse or perivascular collections of inflammatory cells and the possibility of distinguishing these from the lesions recently described in rheumatoid arthritis.

It immediately became apparent that such lesions may be encountered in many diseases. They occurred most commonly in dermatomyositis, disseminated lupus erythematosus, periarteritis nodosa and rheumatoid arthritis. No cases of generalized scleroderma were available for study, but similar lesions have been described in that disease.[6] They have also been reported in cases of rheumatic fever,[4b] but none was seen in this series.

On the basis of a possible common denominator, this group of diseases has frequently been referred to in the recent literature [7] as the "collagen diseases." While classic cases in the group are readily differentiated, borderline types may offer considerable difficulty in diagnosis. To resort to biopsy of muscle for purposes of diagnosis in such cases obviously is of doubtful value unless specific and character-

6. (*a*) Black-Schaffer, B.: Am. J. Path. **22**:647, 1946. (*b*) Weiss, S.; Stead, E. A.; Warren, J. V., and Bailey, O. T.: Arch. Int. Med. **71**:749, 1943.

7. Klemperer, P.; Pollack, A. D., and Baehr, G.: J. A. M. A. **119**:331, 1942. Banks, B. J.: New England J. Med. **225**:433, 1941. Rheumatoid Arthritis, Am. J. Med. **1**:675, 1946.

istic lesions are present. At best the results of biopsy may be used only as confirmatory evidence to support careful clinical observations.

Lesions which may be indistinguishable on microscopic examination from those observed in the diseases mentioned were found in this series and have also been observed by others, in Addison's disease,[8] hyperthyroidism,[9] myasthenia gravis,[6a] fascioscapulohumeral atrophy, subacute combined degeneration, peripheral neuritis and subacute bacterial endocarditis. In most of these an inflammatory factor usually is not considered. Diseases in the latter group are etiologically unrelated and clinically more distinct, and offer less difficulty in diagnosis.

An evaluation of the significance of the lesions described is not a simple problem. They do not appear to be specific for any one disease nor even for diseases of common causation. It is unlikely that they represent the presence of a specific infective agent; they probably are related to a profound metabolic disturbance of muscle or collagen tissue. The fact that these lesions are present in muscles which show little evidence of atrophy and absent, in many cases, in muscles showing considerable degeneration, even though the disease is still active and of short duration, indicates the lack of relationship of the two changes.[10]

SUMMARY

Inflammatory lesions of skeletal muscle of the type which have recently been described in patients with rheumatoid arthritis may be found in a variety of diseases. A study of tissues obtained in a series of routine and selected cases revealed that such lesions occur in patients with rheumatoid arthritis, dermatomyositis, periarteritis nodosa, disseminated lupus erythematosus and subacute bacterial endocarditis. Indistinguishable lesions were also encountered in cases of Addison's disease, hyperthyroidism, myasthenia gravis, fascioscapulohumeral atrophy, subacute combined degeneration and peripheral neuritis. The lesions were marked by focal, perivascular or, occasionally, more diffuse collections of cells. They were situated in ehe endomysium with infiltrations extending between individual muscle fibers, or in the perimysium between the muscle bundles. The cells were mainly lymphocytes and a few plasma cells. Polymorphonuclear leukocytes, eosinophils and large, pale mononuclear cells were present in varying proportions. The lesions are regarded as nonspecific in character, and they showed no constant relationship to the degree of degenerative change present in the muscle.

8. Duff, G. L., and Bernstein, C.: Bull. Johns Hopkins Hosp. **52**:67, 1933.
9. Thorn, G. W., and Eder, H. A.: Am. J. Med. **1**:583, 1946.
10. Mallory, T. B.: New England J. Med. **236**:440, 1947.

PLASMA CELL MASTITIS

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PLASMA cell mastitis was described by Cheatle and Cutler [1] in 1931 and recognized as a clinical and pathologic entity by Adair [2] and Ewing in 1933. Since then 45 cases of the disease have been formally reported or have been mentioned in discussions.[3] In none of these was the mastitis associated with carcinoma of the mammary gland. In 1947 Gaston [4] reported 3 additional cases of plasma cell mastitis, 2 with unusual complications: One of the patients had a sanguinous discharge of the nipple, and in the other "there was a coexistent comedocarcinoma which had metastasized to the axillary nodes." Within the past two years 3 patients with plasma cell mastitis have come to our attention. In addition, in 3 patients with carcinoma of the mammary gland an inflammatory reaction in which plasma cells predominated was observed, so that the coexistence of the plasma cell mastitis and the carcinoma was seriously considered. The problems of the diagnosis and treatment of plasma cell mastitis are well illustrated in these cases; therefore, our observations are presented in some detail.

REPORT OF CASES

CASE 1.—A 66 year old widow was admitted to the University of Oklahoma Hospitals Sept. 24, 1946. She complained of a mass in the right breast of about three weeks' duration. About three months previously she had fallen through the rungs of a ladder and sustained multiple contusions. She did not, however, recall specifically that her breast was injured. She had three children, all living and well. She passed the menopause at the age of 48.

At the time of admission she was rather obese and appeared younger than her age. The mammary glands were of about equal size and shape. The right nipple was retracted. The surrounding skin had a slight "pigskin" appearance

From the Departments of Pathology, Surgery and Histology and Embryology, University of Oklahoma School of Medicine.

1. Cheatle, G. L., and Cutler, M.: Tumors of the Breast, Philadelphia, J. B. Lippincott Company, 1931, p. 298.

2. Adair, F. E.: Arch. Surg. **26**:735, 1933.

3. Parsons, W. H.; Henthorne, J. C., and Clark, R. L., Jr.: Arch Surg. **49**:86, 1944.

4. Gaston, E. A.: Surgery **21**:208, 1947.

and was reddened and tender over an area 8 cm. in diameter. Beneath the skin and apparently attached to it, a firm, irregular mass about 4 cm. in diameter was felt. In the axilla three slightly enlarged lymph nodes were palpable. Urinalysis gave essentially negative results. The red blood cell count was 4,500,000; the hemoglobin content, 12.5 Gm. The white blood cell count was 10,000, with neutrophils 74 (stabs 4), eosinophils 6, lymphocytes 16 and monocytes 4 per cent. Roentgenologic examination of the chest disclosed no neoplastic involvement. On September 26, the mass was incised and examination made of a frozen section. When a diagnosis of chronic inflammatory reaction and no cancer was returned, simple mastectomy was performed. The operative wound healed, and the patient was discharged October 4. When she was seen about one year later there was no recurrence.

Description of Specimen.—The amputated right mammary gland measured 20 by 16 by 5 cm. and weighed 740 Gm. The skin covering the surface was 19 by 13 cm. The nipple was in the center and level with the skin surface. The areola was inconspicuous. A firm mass, 4 cm. in diameter, was located beneath the areola. From the cut surfaces soft creamy material could be expressed, forming molds 0.2 to 0.4 cm. in diameter.

Microscopic preparations from various parts of the involved area disclosed distended lumens of acini and ducts filled with an amorphous pink material. Other lumens contained many large mononuclear cells with foamy cytoplasm. Still others were almost obliterated. Surrounding the lumens there was dense cellular infiltration, with many plasma cells (fig. 1), some lymphocytes and some large mononuclear cells participating. Elsewhere the loose or more dense connective tissue containing the lumens was densely infiltrated with lymphocytes, many plasma cells, large mononuclear cells with foamy cytoplasm, and occasional giant cells of the foreign body type. In places a necrotic debris contained cellular and nuclear fragments of granulocytes and was surrounded by granulation tissue.

Case 2.—A 42 year old housewife was admitted to St. Anthony Hospital, Oklahoma City, Sept. 18, 1946. She complained of a lump in the right breast of about six years' duration. The lump was felt particularly during menstruation, and for the past year there had been an intermittent creamy yellow discharge of the nipple during menstruation. She had one child, 7 years old, living and well.

At the time of admission the patient was well nourished and not obese. The right mammary gland was enlarged to almost twice the size of the left. Two masses were palpable: one beneath the nipple, 6 by 5 by 3 cm., and one in the lower half of the gland, 3 by 3 by 2 cm. The masses were firm and easily movable, unattached either to the underlying tissues or to the skin. The skin was not wrinkled but rather appeared somewhat stretched over the masses. The nipple was not distorted. A thick creamy liquid could be expressed. Three nodular areas were felt in the left mammary gland. These were discrete and measured 1 to 2 cm. in diameter. The lymph nodes of both axillas were palpable. Urinalysis gave essentially negative results. The red blood cell count was 4,060,000; the hemoglobin content, 11 Gm. The white blood cell count was 11,300, with neutrophils 70 and lymphocytes 30 per cent. Simple right mastectomy was performed. The patient was discharged on the seventh day following operation with the wound healed. When she was seen about one year later, there was no recurrence of symptoms.

Description of Specimen.—The amputated right mammary gland was rather large and contained beneath the nipple one mass, 6 by 5 by 3 cm., and in its

lower half another, 3 by 3 by 2 cm. Apparently uninvolved mammary gland tissue surrounded the masses. On the cut surfaces these masses had a variegated appearance with creamy and opaque yellow fields. Dilated ducts contained a thick putty-like material which on pressure yielded molds up to 0.4 cm. in diameter.

Microscopic preparations disclosed various-sized, irregularly spaced lumens lined by flat or cuboidal, partly desquamated cells with foamy cytoplasm. Others were filled with a pink-stained amorphous material, streaked and vacuolated. In the surrounding connective tissue there were regions densely infiltrated by lymphocytes, many plasma cells and some large mononuclear cells. In areas composed of adipose tissue there were streaked, amorphous fields resembling fatty acid crystals surrounded by dense aggregations of large mononuclear cells with foamy cytoplasm and occasional giant cells of the foreign body type. Within these areas of fat necrosis there were dense concentrations of lymphocytes and many plasma cells.

Case 3.—A 51 year old white woman was admitted to the University of Oklahoma Hospitals July 8, 1948. One and one-half years previously she had noted a clear, watery fluid coming from the nipple of the right breast which lasted for one month, then subsided. She remained asymptomatic until six months prior to admission, when a similar fluid appeared from the left nipple. This discharge also subsided spontaneously after about one month. Three weeks before admission she noted a lump in the left breast and a thick yellow material being discharged from the nipple. She had undergone fifteen pregnancies with three miscarriages and had twelve children.

At the time of admission the patient was well nourished. Both mammary glands were pendulous and of about equal size. Both nipples were retracted. There was no discharge of either. In the upper inner quadrant of the left mammary gland there was a firm, tender, irregularly nodular mass 8 cm. in diameter. The mass seemed not to be fixed to the underlying tissues nor to the overlying skin. The axillary lymph nodes were not palpably enlarged. No masses were present in the right mammary gland. Urinalysis gave essentially negative results. The red blood cell count was 4,820,000; the hemoglobin content, 13.5 Gm. The white blood cell count was 7,350, with neutrophils 76, lymphocytes 23 and eosinophils 1 per cent. The Mazzini test of the blood was negative. Roentgenologic examination of the chest disclosed no neoplastic involvement. On July 12 the mass was incised and examination made of a frozen section. When the diagnosis of chronic inflammatory reaction was returned, simple mastectomy was performed by Dr. Hal A. Burnett. The postoperative course was uneventful, and the patient was discharged July 17.

Description of Specimen.—The amputated left mammary gland measured 19 by 18 by 6 cm. The skin covering the surface was 19 by 13 cm. The nipple was in the center, measured 0.8 cm. in diameter, was depressed 1 cm. below the surface and was surrounded by an areola 2 cm. wide. A firm mass about 8 cm. in diameter was felt in the upper inner quadrant. On the cut surfaces the mass was irregularly circumscribed and contained various-sized spaces up to 1.5 cm. in diameter. These were filled with a debris. There were also mottled gray, yellow and red areas. In the surrounding mammary gland tissue the lumens of ducts were conspicuous and were filled with a putty gray semisolid material which on pressure projected as molds up to 0.6 cm. in diameter.

Microscopic preparations disclosed spacious ducts lined by flat or cuboidal cells. The lumens contained a streaked or vacuolated coagulum. Surrounding the ducts

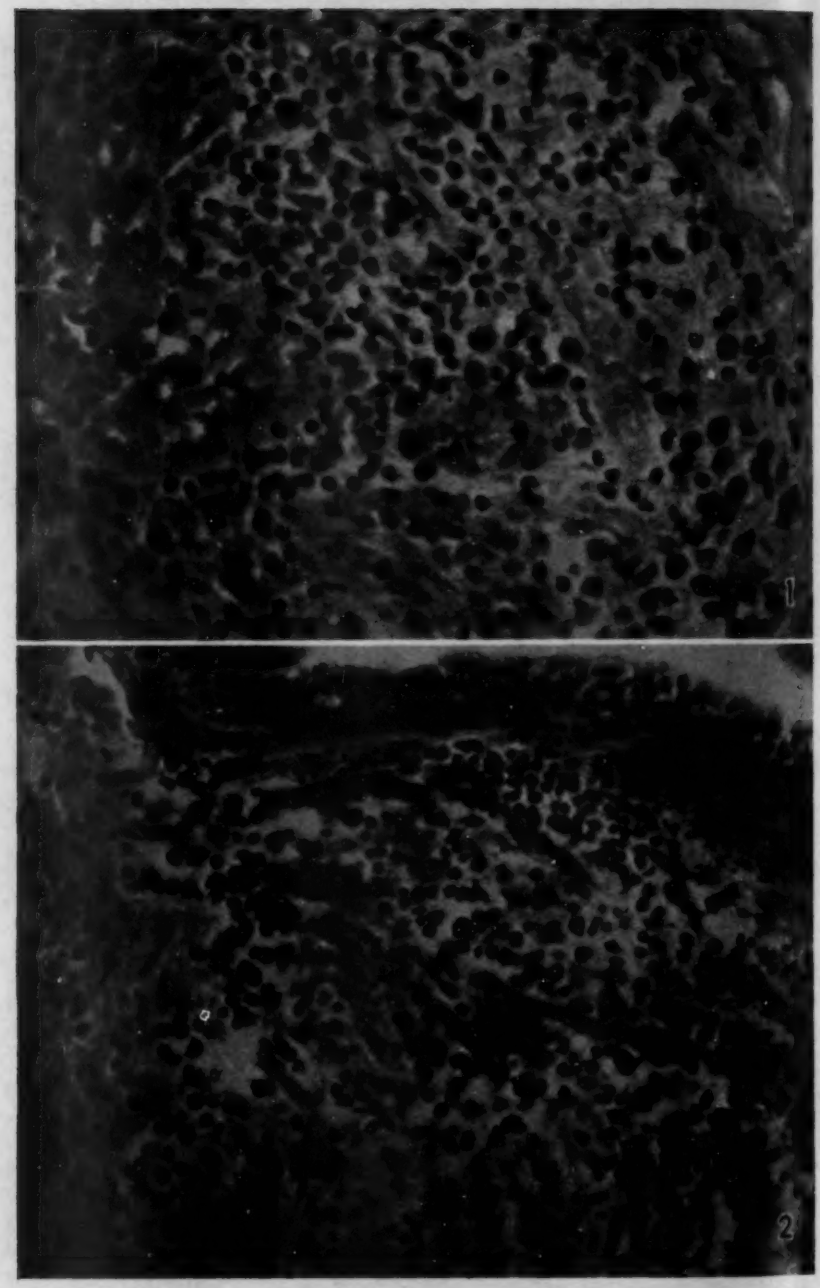

Fig. 1.—Plasma cell mastitis in a woman aged 66. Surrounding the lumen of a duct there is a dense concentration of plasma cells, some lymphocytes and a few large mononuclear cells. × 200.

Fig. 2.—Plasma cell reaction in the mammary gland of a Negro woman aged 63 with carcinoma of the mammary gland. × 200.

and groups of acini in focal areas there were aggregations of lymphocytes, many plasma cells and occasional large mononuclear cells. Elsewhere an area of necrosis extended into the lumen of a duct which contained many large mononuclear cells, a tissue debris with some neutrophilic granulocytes and their nuclear fragments. A zone of infiltration with many plasma cells and lymphocytes surrounded such an area. Areas of fat necrosis with the usual cellular reaction were more extensive in some preparations than in others.

Case 4 is included with the permission of Dr. Lauren V. Ackerman, pathologist, Ellis Fischel State Cancer Hospital, Columbia, Mo.

CASE 4.—A 63 year old Negro woman was admitted to the Ellis Fischel State Cancer Hospital May 24, 1943. She complained of a lump in the left breast of four months' duration. For the last two weeks prior to admission her breast increased in size and became painful, and she had fever. At the time of admission she was rather obese. The left mammary gland was enlarged, the nipple was slightly retracted and excoriated. There was a peau d' orange appearance of the skin around it for a radius of 7 cm. The axillary lymph nodes were not palpably enlarged. A biopsy revealed an inflammatory reaction with collections of plasma cells. A mastectomy with removal of the axillary contents was performed by Dr. H. Everett Sugarbaker. The wound healed without complications. There was no recurrence thirty-eight months later.

Description of Specimen.—The resected left mammary gland contained in its deeper portion a firm mass, 4 by 3 by 3 cm.

Microscopic preparations from various parts of the mass disclosed sheets of neoplastic epithelial cells in a newly formed, loose connective tissue stroma. The cell nuclei were large and vesicular, with a number in varying stages of cell division. About many of the lumens of acini and ducts of the mammary gland there were dense concentrations of lymphocytes, some large mononuclear cells and many plasma cells (fig. 2). The infiltrating plasma cells were usually more conspicuous in the fields not involved in the neoplastic process than in those involved. Two of 29 lymph nodes examined contained tumor metastases.

CASE 5.—A 55 year old woman was admitted to the University of Oklahoma Hospitals Jan. 29, 1947. She complained of an ulcerated lesion of the right breast of three months' duration. Before ulceration a mass had been felt in the right breast for five months. Since then it had increased in size rapidly, and she had progressively lost weight and strength. She was the mother of six children, living and well (ages not available). Menstruation ceased at the age of 44 years.

At the time of admission the patient was thin, cachectic, weighing 92 pounds. In the upper outer quadrant of the right mammary gland there was an area of ulceration, 6 by 5 cm., with elevated and everted hard borders 1 to 2 cm. thick. The right axillary lymph nodes were palpably enlarged. Urinalysis gave essentially negative results. The red blood cell count was 4,450,000; the hemoglobin content, 13 Gm. The white blood cell count was 7,850, with neutrophils 76 (stab forms 17), lymphocytes 18 and mononuclears 6 per cent. The Mazzini test of the blood was negative. Roentgenologic examination of the chest disclosed no pulmonary involvement. Biopsy of the border of the ulcer revealed carcinoma. On February 5, amputation of the right mammary gland was performed by Dr. Harrell C. Dodson. The postoperative course was uneventful, and the patient was discharged on February 17, with the operative wound healed.

Description of Specimen.—The amputated mammary gland measured 17 by 11 by 7 cm. and weighed 420 Gm. The nipple was in the center of the elliptic portion of skin, 17 by 10 cm. It measured 1 cm. in diameter and appeared raw.

Upward and laterally to the nipple there was an ulcerated area, 6 by 4 cm. The margins of the defect in the skin were elevated and firm. Underlying this region and the nipple, there was a firm mass, 5.5 by 5 by 3 cm. On the cut surfaces the mass appeared sunken below the level of the surrounding tissue and was gray-white, dotted with opaque and fibrillar areas. Strands of gray-white tissue radiated from the mass into the surrounding tissue. In the nearby adipose tissue several globular masses, 0.7 to 2 cm. in diameter, were located. These were identified as lymph nodes with neoplastic involvement.

Microscopic preparations from the mass disclosed sheets of neoplastic epithelial cells having large, vesicular, deeply stained nuclei with some in varying stages of cell division. The cell nests were within a loose or more dense, hyalinizing fibrous connective tissue stroma. In the central portions of the large cell nests there were extensive areas of necrosis. The neoplastic cells were seen invading and replacing adipose tissue. Within the connective tissue stroma there were areas infiltrated by lymphocytes, some large mononuclear cells and many plasma cells. About the mammary gland acini and ducts and in streaks within the stroma elsewhere there were dense plasma cell infiltrations. In preparations from the lymph nodes only streaks of lymphatic tissue remained; the rest was replaced by neoplastic cells and their stroma.

CASE 6.—A 60 year old white woman was admitted to the University of Oklahoma Hospitals Nov. 3, 1947, complaining of a mass in the left mammary gland. In 1937 there had been some discharge of the nipple. At that time she noticed a mass about 2 cm. in diameter in the same mammary gland. After about six years the mass began to increase in size. In July 1947, the growth was almost 10 cm. in diameter, and erosion of the skin began and progressed toward the nipple. The patient had undergone ten pregnancies with six miscarriages and had four children living and well.

At the time of admission she was slightly obese, with no obvious loss of weight. The mammary glands were large and pendulous, with the left somewhat larger than the right. Underlying a granular excoriated area of the skin 2 cm. in diameter involving the nipple and extending upward and laterally, there was a hard, irregular mass, 8 by 8 cm. The mass was in the outer portion of the mammary gland and not attached to the chest wall. The axillary lymph nodes were not palpable. There were no masses in the right mammary gland. Examination of the urine gave essentially negative results. The red blood cell count was 3,650,000; the hemoglobin content, 12 Gm. The white blood cell count was 11,800, with neutrophils 65, lymphocytes 23, monocytes 10 and eosinophils 2 per cent. The Mazzini test of the blood was negative. Roentgenograms of the chest revealed no pulmonary metastasis. On November 5, after a diagnosis of carcinoma was returned on examination of a frozen section, radical mastectomy was performed by Dr. Harrell C. Dodson. When the patient was seen March 3, 1948, there was no recurrence.

Description of Specimen.—The amputated left mammary gland weighed 2,160 Gm. An elliptic portion of skin, 24 by 14 cm., covered the anterior surface. The nipple was located near the center. It was retracted to 0.2 cm. above the surface and was excoriated, with the areola inconspicuous. Beneath the nipple there was a firm mass, 6 cm. in diameter, which on the cut surfaces appeared sunken below the level of the surrounding tissues with streaks of gray-white tissue radiating from it. In the remaining portions of the mammary gland there were lumens up to 0.4 cm., yielding putty-like molds on pressure.

Microscopic preparations from the mass disclosed sheets and nests of neoplastic epithelial cells with vesicular or compact, deeply stained nuclei in a pink-stained

or halo-like cytoplasm, within a connective tissue stroma. Elsewhere the cells were within tissue or lymph spaces. Surrounding the remains of mammary gland acini and ducts and also about the neoplastic cell nests there were dense concentrations of lymphocytes, many plasma cells and some large mononuclear cells. Necrosis was seen within the neoplastic areas. Areas of fat necrosis were absent. Ten lymph nodes examined were free of neoplastic involvement.

COMMENT

Plasma cell mastitis may be redefined as a focal chronic inflammatory process in the mammary gland. Plasma cells are dominant in the inflammatory process and far outnumber all the other cells participating in the reaction. The cause of the lesion is as yet unknown.

Multiple areas of fat necrosis often accompany plasma cell mastitis. In our 3 cases of plasma cell mastitis there were areas of fat necrosis. Either fat necrosis as such or plasma cell mastitis alone or both in combination form a solid mass, indefinitely delineated, not unlike carcinoma.

In our 3 cases of carcinoma of the mammary gland there was a cellular reaction in which plasma cells predominated. The fact, however, that most of the cellular reaction was about the acini and ducts of the mammary gland and in areas distant from the neoplastic involvement favors the view that the plasma cell reaction was independent of the carcinoma.

An accurate history may aid in the differential diagnosis. A firm mass appearing in the mammary gland following trauma and persisting for years with no appreciable change in size suggests fat necrosis. A firm mass appearing in the mammary gland without a history of trauma and persisting for years with no appreciable change in size suggests plasma cell mastitis. A sudden increase in the size of either type of mass points toward a combination with carcinoma. In any event the nature of the mass can be determined only by microscopic examination. Diagnosis by frozen section, however, can be accurate only if a representative portion of tissue is examined. Radical operation is indicated only in case the mass proves to be cancerous.

SUMMARY

Plasma cell mastitis is defined as a focal chronic inflammatory process in the mammary gland, frequently associated with areas of fat necrosis. Plasma cells are dominant in the inflammatory process and far outnumber all the other cells participating in the reaction. The cause of the lesion is as yet unknown.

Clinical data are presented, concerning 3 patients with plasma cell mastitis and 3 patients with carcinoma of the mammary gland in whom there was a cellular reaction with plasma cells predominating about acini and ducts believed to be independent of the carcinoma.

A QUANTITATIVE APPROACH TO THE STUDY OF SPLENOMEGALY

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STUDIES of the morbid anatomy of splenomegaly have hitherto been confined to an analysis of the general structure of the spleen and the finer cytologic details. Approximate estimates of the percentages of white pulp, red pulp and trabecular system are a corollary to an appraisal of the lesion. Because of the obvious inaccuracy of such haphazard estimates, it was thought that an exact quantitative determination of the constituents of the spleen might yield information regarding the nature and the evolution of the morbid process.

In general, enlargement of any organ can be conceived as the response to a stimulus. Enlargements occurring under morbid conditions can be classified into different groups according to the textural alterations which can be recognized by anatomic-histologic investigation. Broadly speaking, an organ may increase in size if it is the seat of inflammation or of neoplastic growth, or if its constituent elements increase in number (hyperplasia) or in size; the latter type of enlargement may be due to hypertrophy of the organ or to its being infiltrated with products of metabolism.

The same principle of morphogenetic classification can be applied to enlargements of the spleen. However, the identification and the separation of the individual groups are far more complicated in the case of the spleen than in that of any other organ of the body. This difficulty is partly explained by the intricacy of the splenic structure and the complexity of its cellular constituents under normal and particularly under morbid conditions. It is accounted for, furthermore, by the observation that the basic cellular constituents of the spleen, which can adequately be designated as the parenchyma of the organ, react with similar proliferation to dissimilar stimuli. A pathogenetic appraisal of splenic enlargement can therefore not be founded on the simple

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morphogenetic analysis which applies to other organs. It must correlate the relative augmentation of the various cellular elements with the respective alteration of the splenic structure observed in splenomegalies of obviously different, but defined, etiology. In this manner criteria have been established which permit one to make a tentative morphologic classification of splenomegalies on a dynamic basis.

As in any other organ, so in the spleen structure and function are mutually dependent. The main splenic functions can be divided into those of metabolism (including defense against infection), blood storage and blood cell formation. The reservoir function of the spleen is obviously associated with the structural pattern of the red pulp, while the formation of blood cells seems to be divided between the red and the white pulp. Which of these portions is more prominently engaged in defense reactions is not so obvious from a consideration of the normal spleen. Alterations of the splenic structure must reflect alterations of function, so that it seems justified to assume that a prominent enlargement of one of the main constituents of the spleen (i. e., red and white pulp) can be regarded as the result of an increased functional stimulation. For this reason the quantitative analysis of various forms of splenomegaly appeared to be indicated.

It was obvious that first such forms had to be selected in which the pathogenic factor responsible for enlargement was clear. It was to be expected that in some of these groups the results of the laborious measurements could have been anticipated from the gross appearance of the spleen. But by proceeding in these investigations from the known to the unknown, it was hoped that observations could be made which might indicate which of the splenic partitions was prominently involved. Such results could then point the way to inclusion or exclusion of certain factors hitherto prominently considered in the explanation of the pathogenesis of the particular form.

This report is concerned with the modification of a method for the quantitative estimation of the percentages of white pulp, red pulp and trabeculae, together with a consideration of the results obtained in a group of representative splenomegalies. In the mathematical analysis of the material, measurements had to be made of the white pulp and of the trabeculae, and the amount of red pulp was then arrived at by subtraction.

It was apparent at the outset that many difficulties would arise and that the results might not be statistically significant.

The pioneer work in this field was done by Hellman,[1] who obtained the percentage composition of normal spleens at various ages. He measured white pulp, red pulp and stroma in 100 cases of sudden death.

1. Hellman, T.: Ztschr. f. Konstitutionslehre **12**:270, 1926.

Under the stroma he included trabeculae, capsule and blood vessels. He also measured the area of the germinal centers (secondary follicles).

His method was to project microscopic fields onto paper of uniform composition and thickness, trace and cut out the various components, and determine their percentages by weighing the paper.

Under the white pulp he included the malpighian corpuscles and perivascular lymph sheaths. His percentage weights for white pulp and connective tissue are shown in table 1.

Using a technic similar to Hellman's, von Herrath [2] obtained the percentages of the various constituents of spleens of various mammals, including man. Only 22 spleens were thus examined, 2 of which were human. The figures are therefore statistically not significant. For

TABLE 1.—*Percentage Weights of the White Pulp and the Connective Tissue as Determined in Normal Spleen by Hellman*

Age Group	White Pulp	Connective Tissue
Fetuses	9.55	1.97
Newborn infants	10.69	3.37
0-1 yr.	20.96	4.03
2-5 yr.	21.49	5.74
6-10 yr.	19.63	6.20
11-15 yr.	15.66	6.46
16-20 yr.	13.67	5.97
21-30 yr.	9.63	6.91
31-40 yr.	9.53	7.82
41-50 yr.	8.27	9.58
Over 50 yr.	6.43	11.07

TABLE 2.—*Percentages of the White and the Red Pulp and the Trabeculae as Observed in Two Human Spleens by von Herrath*[2]

Case	White Pulp	Red Pulp	Trabeculae
1	18.93	74.01	7.06
2	17.45	78.08	4.47

purposes of comparison, however, the results which he obtained in his 2 human cases are quoted. (The ages of the patients were not stated.)

Hwang, Lippincott and Krumbhaar [3] studied the percentage areas of white pulp in 300 normal human spleens of various ages. Their particular purpose was to check the correlation between white pulp and age. They also counted the number of follicles per unit area and measured the areas taken up by the pale-staining centers of follicles plus the central arteries. Their method was apparently less cumbersome than that of the previous authors. They projected the microscopic field onto a piece of paper, traced the limits of the tissues to be estimated, and measured the areas with a planimeter.

2. von Herrath, E.: Ztschr. f. mikr.-anat. Forsch. **37**:389, 1935.

3. Hwang, J. M. S.; Lippincott, S. W., and Krumbhaar, E. B.: Am. J. Path. **14**:809, 1938.

They found that the amount of lymphatic tissue (including germinal centers and central arteries) was small in infants (4.8 per cent up to 1 year of age), rose to a maximum in the first decade (12.1 per cent), then dropped sharply (8.6 per cent, the mean for the decade 11 to 20) and continued at about that level (chart 1). After subjecting their results to statistical analysis, they stated that if the groups from 11 years on were considered, the line was not significantly different from horizontal, although it did have a slightly downward trend. They detected the suggestion of an increase in the percentage of lymphatic tissue in the sixth and seventh decades, with a drop thereafter.

It is evident that certain correlations exist between the age and the percentage composition of the spleen. If in our studies the abnormal spleens were to be compared with controls of the same age group, the

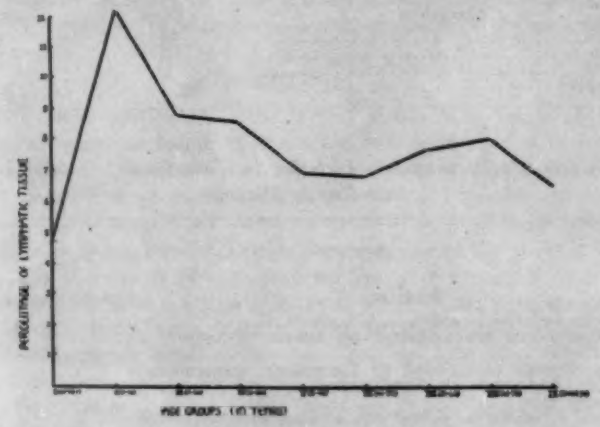

Chart 1.—Percentage of follicular lymphatic tissue at various ages (after Hwang, Lippincott and Krumbhaar [3]).

amount of work involved would be prohibitive, and the material available insufficient. Therefore, since the greatest age variations exist in childhood, we sought to determine whether, by using only subjects over 21, it would be valid to pool all the ages in the final computations.

The answer was in the affirmative. It has already been mentioned that Hwang and associates [3] found that the percentage of lymphatic tissue was relatively constant for the years over 11. As their paper did not include all the figures, this conclusion could not be checked. However, using Hellman's [1] statistics, we determined that for the ages over 21 there was no correlation between age and the percentage of white pulp. (The correlation coefficient was 0.28, with a standard error of 0.12.)

A different situation existed in regard to the connective tissue, for there Hellman's figures showed an increase with age (table 3, adapted

from his table 24). This point must be borne in mind in interpreting the final results of our calculations. However, as will be seen subsequently, the average ages of our controls were not markedly different from those of the patients with splenomegaly. The error from this source is therefore minimized.

MATERIAL

Normal Spleens.—Thirty "normal" spleens were obtained through the courtesy of Dr. Milton Helpern and Dr. Jacob Werne, Medical Examiners, New York. They were obtained in cases of sudden (violent or accidental) death in which no

TABLE 3.—*Percentage Areas of Connective Tissue Determined for Age Groups by Hellman*[1]

Age Group	Cases	Connective Tissue, per Cent
21-30	23	6.91
31-40	17	7.82
41-50	12	9.58
Over 50	7	11.07

TABLE 4.—*Cases of Splenomegaly Included in This Study, Divided into Classes According to Diagnoses*

Diagnosis	Cases	Average Age, Yr.	Average Wt. of Spleen, Gm.
Subacute bacterial endocarditis	15	43	500
Laennec's cirrhosis (uncomplicated by disease of splenic or portal vein)	17	47	513
Laennec's cirrhosis complicated by thrombosis, thrombophlebitis, phlebosclerosis or carcinomatous invasion of portal or splenic vein	9	54	619
Obstruction of splenic or portal vein without cirrhosis of the liver (thrombosis, phlebosclerosis, cavernomatous transformation or extrinsic pressure on the portal or splenic veins)	8	53	731
Leukemia (acute and chronic myeloid types)	8	48	1,691
Chronic cardiac failure	6	48	410
Polycythemia vera (1 case with thrombosis of portal, splenic and hepatic veins)	5	59	1,229
Gaucher's disease	3	39	1,333

history or autopsy findings were present to suggest any antecedent disease. The subjects were all over 21 years of age, were of both sexes and belonged to the white and the Negro race. No attempt was made to segregate them according to sex or race. Body weight was not considered. The average age of these controls was 43; the mean weight of the spleen was 128 Gm.

Diseased Spleens.—Both postmortem and surgical material was used. No cases were included in which the diagnosis was in doubt. A specimen removed at operation was utilized only if the diagnosis was either clear at operation or subsequently confirmed by postmortem examination. All the patients were over 21 years of age. No distinction of sex or race was made. Table 4 summarizes these details of the included cases.

It is apparent that, whereas some of the groups are fairly homogeneous, others vary considerably in their pathogenesis. In general, an attempt was made to

include in each group diseases which would be expected or are known to exert similar effects on the spleen.

Subacute bacterial endocarditis was chosen as the prototype of a chronic infectious disease, while obstruction of the portal or the splenic vein was considered representative of the group ascribed to hemodynamic influence.

As far as possible, an attempt was made to exclude cases in which the primary disease was complicated by a pathologic process which might have an effect on the spleen. As an example, the presence of long-standing cardiac failure would exclude from consideration a case of subacute bacterial endocarditis.

Because the choice of spleens was limited, it was impossible to take into consideration the duration and the extent of the disease process.

The relatively small number of cases included in each group was dictated both by the paucity of available material and by the time-consuming nature of the work. To this one factor alone (i.e., the paucity of samples) are probably attributable the failure to obtain results of statistical significance in many instances. However, in regard to certain diseases, such as polycythemia vera and Gaucher's disease, it was only necessary to examine a few spleens to obtain significant figures. This could be predicted in advance by a consideration of the extensive changes in the spleen.

METHODS

Usually a large section of each normal spleen was taken at postmortem examination, through the length of the organ and perpendicular to its convexity, and fixed in formaldehyde solution. The specimens of pathologic spleens were taken from material fixed in Kaiserling's solution and usually cut originally as just stated.

From each specimen, three flat slices were cut, measuring about 2 to 3 mm. in thickness. The dimensions of each such section were about 1.5 by 3.5 cm. An attempt was made to take one slice from each pole and one from the center of the spleen. This was not always possible. The sections usually included a portion of splenic capsule at one edge.

Paraffin sections were stained by the hematoxylin-eosin method. Each section was placed on a separate slide, so that there were three slides for each spleen.

The percentage areas of trabeculae and white pulp were measured, and the red pulp made up the difference.

The method was a modification of that used by Hwang and associates.[9]

These authors projected the microscopic field onto a piece of paper, outlined the white pulp and measured the tracings with a planimeter.

In our method one step was eliminated by projecting the field from below onto a piece of translucent paper fixed to a large plate of glass acting as a table. The image could thus be measured directly on the paper without first tracing the outlines.

A horizontally placed carbon arc microscope projector was used, placed on a platform 10 inches (25.5 cm.) high, which rested on the floor. By means of a prism, the image was reflected upward, coming to a focus on a sheet of "onion skin" paper fixed by Scotch tape on the top of the plate of glass. The latter was 31 inches (76 cm.) from the floor. The work was done in a darkened room, and the image thus obtained was clear enough for the purpose. The light traversed the glass plate from below, and the field could be measured directly on the paper from above.

For each area measured it was necessary only to make one dot with a pencil on the periphery as a point of reference for the planimeter. The translucent paper was changed frequently.

The "geographic" objective was used (22.4 mm., 6 ×) and the 10 × ocular. The final magnification was about 90 diameters. The actual diameter of the final image was 8 5/16 inches (21 cm.). All distances were fixed, and thus the magnifications were constant.

To retard overheating and fading of the slide, the source of light for the microscope projector was passed through a glass container of chopped ice and water, which was changed frequently. Despite this, considerable fading and distortion occurred.

In each case, 16 fields were counted, each field representing approximately 0.0066 square inch (0.04 sq. cm.) of spleen; the total was therefore 0.10 square inch (0.65 sq. cm.).

The reasoning by which it was determined to calculate 16 fields was as follows: Using Hellman's figures for white pulp and trabeculae, divided into age groups by decades, we found that the standard deviation for each case reached as high as 40 per cent. With this expected variation, therefore, it was considered that our own accuracy need not be better than 30 per cent. One of our cases was then taken as a sample, and the percentages of trabeculae and white pulp determined by measuring 20 fields. From these figures it was then possible to determine the standard deviation, and it was calculated that a standard error of 30 per cent for the trabeculae and 15 per cent for the white pulp would obtain when 16 fields were measured. As the later computations showed, an accuracy of better than 30 per cent was actually achieved in each case.

As it had been shown previously that the malpighian corpuscles are uniformly distributed throughout the spleen,[4] and that the same probably holds true for the trabeculae,[2] the 16 fields were taken at random, except that the capsule was avoided. Usually 5 or 6 fields were measured in each of the three sections.

In measuring lymphatic tissue, considerable difficulty was encountered, as was expected, and the error therefore was considerable. All aggregates of lymphocytes were measured which were sufficiently large and concentrated to give a distinct blue area on the screen. Most of these areas were malpighian corpuscles and collections about blood vessels, but occasionally isolated collections of cells also occurred. Many of the latter probably represented follicles cut through their peripheries.

More often than not the limits of the lymphatic tissue were not sharp and the borders taken were arbitrary ones. Such borders were usually taken around the periphery of the dense zone. The measurements were all done by the same person and in the same fashion, so that the error from this source was minimized.

No attempt was made to separate the germinal centers from the remaining lymphatic tissue. When blood vessels and their adventitial sheaths within lymphatic collections amounted to more than half of the area in question, they were included with the trabeculae rather than the lymphatic tissue. This, of course, was also an arbitrary rule.

Unavoidable errors were introduced by artefacts, such as shrinkage, slight cracking and the separation of the tissue sections.

The measuring of the trabeculae was easier, because the borders were usually well defined. Blood vessels larger than capillaries were included with the trabeculae.

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4. Hellman.[1] Hwang and others.[3]

STATISTICAL TREATMENT

Individual Spleens.—For each of the sixteen fields the area of white pulp and that of trabeculae were obtained separately. The mean area per cent was then calculated. The standard deviation of each measurement and the standard error were then obtained by means of the formulas:

$$\sigma = \sqrt{\frac{\Sigma(s^2)}{n-1}} \qquad (1)$$

$$\sigma_e = \frac{\sigma}{\sqrt{n}} \qquad (2)$$

where

σ = the standard deviation of a single measurement
s = the difference of each measurement from the arithmetic mean
n = the number of cases
σ_e = the standard error (which is also referred to as standard deviation of the mean)

The final figures for an individual spleen would then appear, for example:

Trabeculae	3.99% ± 0.6% (standard error)
White pulp	9.25% ± 1.16
Red pulp	100-3.99-9.25 — 86.76%

Groups of Spleens.—For each group (i. e., normal spleens, spleens obtained in cases of Laennec's cirrhosis, etc.) the percentages were totaled, the mean percentage obtained for the entire group, and the standard deviation obtained by the formula[5]:

$$\sigma = \sqrt{\frac{\Sigma(X)^2}{n} - \bar{X}} \qquad (3)$$

where

σ = the standard deviation

n = the number of cases in the group

$\Sigma(X)^2$ = the sum of thesquares of each unit

$\bar{X}$ = the mean for the group.

The standard error was then obtained from the standard deviation by equation 2.

5. This formula is more convenient for calculation of the standard deviation in a larger number of cases (see Arkin, H., and Colton, R.: An Outline of Statistical Methods, New York, Barnes & Noble, 1947, p. 33).

Each group of abnormal spleens was then compared with the control group to determine whether the differences were statistically significant. These calculations involved the white pulp and trabeculae. First, the percentage areas were compared. The difference between the abnormal and the control was taken, and the ratio of this difference to the standard

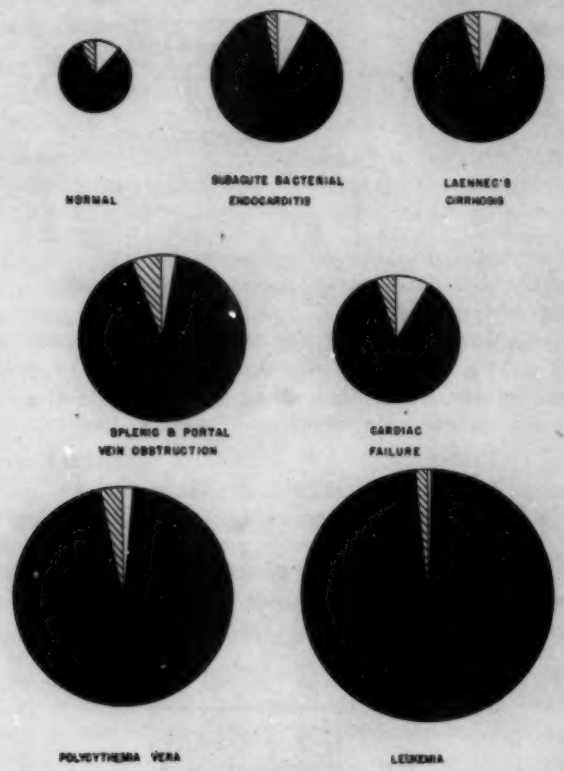

Chart 2.—Diagrammatic representation of the results given in table 5. The area of each circle is proportional to the weight of the spleen. The solid black represents red pulp; the cross-hatched area, trabeculae, and the clear area, white pulp.

error of the difference was calculated (ratio of significance). The standard error of the difference, σ_d, is calculated from the formula:

$$\sigma_d = \sqrt{\sigma_1^2 + \sigma_2^2} \qquad (4)$$

where

σ_1 = the standard error of the value for the controls
σ_2 = the standard error of the value for the pathologic specimens

TABLE 5.—*Percentage Composition of Spleens Obtained in Cases of Splenomegaly Compared with That of Normal Spleens*

		Percentage					Absolute Weight								
Diagnosis	Cases	Trabeculae	S.R.*	White Pulp	S.R.	Red Pulp	Mean Wt.	Index†	Trabeculae	S.R.	Index	White Pulp	S.R.	Index	Red Pulp	Index
Normal	30	6.21	....	11.99	....	81.80	128	...	7.95	....	....	15.32	...	...	105.0	...
Subacute bacterial endocarditis	15	2.79	2.59	8.50	1.11	88.71	500	3.9	13.95	1.47	1.75	42.50	2.3	2.7	443.5	4.2
Laennec's cirrhosis (simple)	17	3.89	1.53	6.22	2.11	89.89	513	4.0	20.00	2.0	2.50	31.95	1.76	2.1	462.0	4.4
Laennec cirrhosis with disease of splenic or portal vein	9	7.29	0.34	5.10	2.36	87.61	619	4.8	45.10	2.16	5.6	31.50	1.34	2.1	542.5	5.2
Obstruction of splenic or portal vein	8	5.91	0.04	2.48	3.96	91.61	731	5.7	43.25	2.05	5.4	18.13	0.38	1.2	670.0	6.4
Leukemia	8	1.44	3.82	0.13	5.31	98.43	1,691	13.2	24.40	1.56	3.0	2.20	6.26	0.1	1,664.0	15.9
Cardiac failure	6	5.09	0.19	9.25	0.67	85.66	410	3.2	20.90	1.36	2.6	37.95	1.30	2.5	351.8	3.4
Polycythemia vera	5	3.37	1.54	1.50	4.52	95.23	1,239	9.67	40.50	1.59	5.1	18.60	0.35	1.2	1,180.0	11.2
Gaucher's disease	3	3.02	1.44	2.04	3.77	94.94	1,333	10.4	40.30	1.31	5.0	27.20	0.69	1.8	1,268.0	12.0

* S. R. = significance ratio.
† Index = ratio of weight of spleen to that of a normal spleen.

For example, if the white pulp of the controls is compared with the white pulp of the specimens obtained in cases of subacute bacterial endocarditis (table 5):

$$\text{Ratio of Significance} = \frac{11.99 - 8.50}{\sqrt{(2.23)^2 + (2.21)^2}} = 1.11$$

It is an elementary theorem of statistics that the probability that the difference between any two sets of results is significant increases as the foregoing ratio rises. If the ratio is 3, the odds are 369.4 to 1 that the difference is significant. When the ratio is less than 1, the difference is not significant. Between 2 and 3 the odds rise rapidly (Pearl [6]).

A further comparison was obtained by approximating the absolute weights of trabeculae, white pulp and red pulp by multiplying the total spleen weights by the percentages of each constituent. The "absolute weights" of the abnormal spleens were then compared statistically with the weights of the normal controls, and the ratio of significance was obtained.

This, of course, is only a rough method of estimating the relative weights of the various constituents of the spleen, because the volumes of the different parts are not directly proportional to the area measured on a cross section. Furthermore, the specific gravities of the morphologic

TABLE 6.—*Comparison of Means Obtained for Components of Normal Spleens by Different Investigators*

	Connective Tissue	White Pulp	Red Pulp
Our figures (30 cases)	6.21%	11.99%	81.80%
Hellman [1] (50 cases)	8.20	9.36	82.44
Hwang, Lippincott and Krumbhaar [3] (253 cases)	....	7.32	

units are not taken into account. The aforementioned figures are therefore only an estimation for purposes of comparison. The results appear in table 5 and chart 2.

SOURCES OF ERROR

Because of several unavoidable sources of error, it was early postulated that in many cases no results of statistical significance would be obtained. These sources of error were (1) the great individual variation of normal spleens,[4] (2) the difficulties of preparing, sampling and measuring the specimens and (3) the small number of cases examined.

PERCENTAGES FOR NORMAL SPLEENS

The only authors who had comparable statistics were Hellman [1] and Hwang and associates.[3] In table 6 the means of all spleens taken from

6. Pearl, R.: Introduction to Medical Biometry and Statistics, ed. 3, Philadelphia, W. B. Saunders Company, 1940.

persons 21 years of age and over recorded in their tables are compared with ours.

In regard to the white pulp, our computation is higher than either of the others. The explanation of this discrepancy probably lies in the fact that we included small aggregations of lymphatic tissue which the others did not consider significant enough to measure. The other source of difference lies in the points chosen for the borders of the follicles. The difference between our percentage of connective tissue and Hellman's probably occurred because he included a portion of capsule.

PERCENTAGES FOR PATHOLOGIC SPLEENS

As is evident from table 5, significant differences from the normal spleens were observed in some cases, and in certain others the results showed no significant differences. In the great majority, however, the results were of doubtful significance, and hence in the following broad interpretation some reservations must be made.

Subacute Bacterial Endocarditis.—The percentage of trabeculae decreases to 2.79 from a normal of 6.21. The ratio of significance is 2.6, indicating that the odds are 106.3 to 1 against this difference being due to chance. As the average age of these spleens is the same as that of the controls, the age factor need not be considered.

The percentage of white pulp is 8.50, compared with a normal of 11.99, which gives a ratio of significance of 1.1. This means that the odds are only 2.69 to 1 against this difference being due to errors of sampling and determination. In other words, the percentage of white pulp does not differ significantly from the normal.

The red pulp comprises 88.71 per cent of the area, compared with the normal 81.80 per cent.

Summary: In this disease the increase of the weight of the spleen is caused by a growth of both the red and the white pulp, but the trabeculae do not keep pace with this growth.

Laennec's Cirrhosis (Uncomplicated).—The percentage of trabeculae is 3.89, compared with a normal of 6.21. The ratio of significance is 1.5, which allows no definite conclusions to be drawn.

The percentage of white pulp is 6.22, with a ratio of significance of 2.11. This comes under the heading "probably significantly decreased."

The red pulp is increased to 89.89 per cent.

Summary: In this disease there is growth of all elements; the red pulp most, the white pulp least. The final ratio indicates some decrease of the percentages of trabeculae and white pulp as compared with normal spleens, with an increase of the percentage of red pulp.

Laennec's Cirrhosis with Pathologic Involvement of Veins.—The trabeculae amount to 7.29 per cent; the ratio of significance is 0.34, which means that the percentage does not differ significantly from the normal. The white pulp is 5.10 per cent, with a ratio of significance of 2.36; hence it is probably significantly decreased.

The red pulp is increased to 87.61 per cent.

Summary: There is growth of all elements, least of the white pulp. The final ratio indicates no change in the percentage of trabeculae, and a definite decrease in the percentage of white pulp.

Laennec's Cirrhosis With and Without Pathologic Involvement of Veins.—The results are essentially the same as in the previous group. (The figures are not shown in table 5.)

Pathologic Involvement of Splenic and Portal Veins.—The trabeculae total 5.91 per cent, with a ratio of significance of 0.04—indicating no significant difference from the normal of 6.21.

The white pulp measures 2.48 per cent, significantly decreased from the normal. The significance ratio is 3.96—a high figure.

The red pulp is increased to 91.61 per cent.

Summary: The increase in weight is due to a growth of trabeculae and red pulp. The white pulp does not grow at all. This is clearly brought out by comparison of the absolute weight of the white pulp (18.13 Gm., compared with the normal of 15.32).

Leukemia.—The figure of 1.44 per cent for trabeculae (significance ratio, 3.82) shows a marked decrease. The white pulp amounts to only 0.13 per cent (significance ratio, 5.31), which means that it practically disappears. This, of course, could have been predicted in advance.

The red pulp rises to 98.43 per cent. (As the average age of the leukemic persons was higher than that of the normal ones, and the trabeculae therefore would be expected to increase, the age factor can again be disregarded.)

Summary: The growth is limited to the red pulp; the white pulp disappears; the trabeculae do not take part in the growth. The absolute weight of the trabeculae remains essentially unchanged.

Cardiac Failure.—The ratios show that the percentages do not differ significantly from normal. There appears to be a proportional growth of all elements.

Polycythemia Vera.—The trabeculae total 3.27 per cent, with a ratio of significance of 1.54. The difference is therefore not significant statistically.

The white pulp drops sharply to 1.50 per cent, indicating a significant decrease from the normal of 11.99 per cent.

The red pulp is high—95.23 per cent.

Summary: The growth is chiefly of the red pulp; there is some growth of trabeculae; the white pulp does not participate in the growth. This is reflected in a significant decrease of the ratio of white pulp, some decrease of that of the trabeculae and an increase of the percentage of red pulp.

Gaucher's Disease.—The result of 3.02 per cent for trabeculae is not definitely significant statistically (significance ratio, 1.44). The white pulp drops significantly to 2.04 per cent (significance ratio, 3.77). The red pulp therefore increases—to 94.94 per cent.

Summary: The results are the same as in polycythemia vera.

COMMENT

It is now possible to examine and perhaps answer some of the questions raised by this investigation. Has anything been discovered about the behavior of the spleen, by this quantitative approach, which was not known before?

The answer to this fundamental question is in the affirmative. When more detailed results are sought, however, it is difficult to know where fact ends and speculation begins.

As indicated previously, the problem is one of a statistical analysis in which the sample is perforce relatively small. This discussion is therefore of a tentative nature and calculated more to provoke further investigation along the same lines than to give unequivocal conclusions.

It can certainly be inferred that the spleen does not increase in size as a whole; that is, its elements do not grow proportionately. This is not a startling conclusion of itself and could have been predicted from a knowledge of the histologic aspects of splenomegaly. However, it has now been demonstrated in quantitative terms.

Since the trabecular system serves a purely supportive function (an assumption borne out by our results), it can profitably be overlooked in the present discussion. From this point of view, splenomegaly is caused in the great majority of cases by growth of the red pulp. In only one disease under study, subacute bacterial endocarditis, do the white pulp, the red pulp and the trabeculae show proportional growth. Indeed, study of the estimated absolute weights of the various constituents (table 5) indicates that in obstruction of the splenic or the portal vein and in polycythemia vera, for example, the white pulp remains completely untouched, as if it were an entirely different organ.

The conclusion is inescapable that the structural units respond independently. There are two corollaries to this: 1. If one interpreted a given disease in terms of these units and what is known of their function one might shed light on the nature of the morbid process. 2. Reasoning

in the reverse direction, one might expect the known nature of certain disease processes to increase knowledge of the functions of the individual constituents of the spleen.

Leukemia and Gaucher's Disease.—As expected, the splenic enlargement in myeloid leukemia is due to an overwhelming growth of the red pulp. There is an actual decrease of the total amount of white pulp, indicating that either it has been destroyed or it has failed to regenerate as it would under normal conditions. The overgrowth of red pulp is easily understood in this disease, in which the reticuloendothelial system becomes involved by virtue of its potentialities as embryonal mesenchyme.

A comparative quantitative study of chronic lymphatic leukemia was not undertaken, because the results could be predicted, and, furthermore, because there was no probability that the malpighian follicles could be differentiated from the red pulp diffusely infiltrated by lymphocytes.

The results in Gaucher's disease are similar to those in leukemia with the one exception that the white pulp fails to disappear. The higher percentage of trabeculae in Gaucher's disease may be a function of the more chronic course of the illness. The results leave no doubt that the red pulp is the site of prominent enlargement by virtue of its metabolic activity.

Polycythemia Vera.—The spleen in polycythemia vera has been described by Delannoy [7] as showing a striking engorgement of the sinuses and a conspicuous cellularity of the red pulp, with but few malpighian corpuscles. Klemperer [8] noted hyperplasia of the cytoplasmic reticulum of the red pulp. The quantitative measurements reveal a significant decrease in the percentage of the white pulp, although the total amount is not as markedly diminished as in myeloid leukemia. In fact, the absolute weight of the white pulp remains unchanged, indicating that it is not affected by this disease. The exclusive proliferation of the red pulp without any evidence of sinus hyperplasia pointing to a circulatory factor suggests that the undifferentiated splenic reticulum has been stimulated but without further hematic differentiation. That the hyperplastic reticulum cells, however, retain their original hemoblastic competence becomes evident in those cases of polycythemia which present final myeloid metaplasia and a leukemic blood picture.

It has been previously suggested that the growth of the trabeculae might be a function of the duration of the disease. If this is so, one would expect that a disease like polycythemia in a leukemoid phase,

7. Delannoy, E.: Un cas de maladie de Vaquez, Paris, G. Doin, 1924.

8. Klemperer, P.: The Spleen, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938.

in which the histologic aspect is similar to that of leukemia but the clinical course is more prolonged, would show a larger percentage of trabeculae. In such a case in which we were able to make measurements, this hypothesis was confirmed. Despite enormous enlargement of the organ (3,900 Gm.), the percentage of trabeculae was 6.13 ± 1.33; the white pulp was completely absent; the red pulp amounted to 93.87 per cent.

Chronic Disturbance of the Circulation of the Blood.—From a consideration of the fact that splenomegaly occurs only occasionally in cardiac failure, it is apparent that increased systemic venous pressure, of itself, does not lead to enlargement of the spleen. Unfortunately, our study of the 6 cases of chronic cardiac failure did not yield percentages differing statistically from the normal. It is possible that investigation of a much larger sample might do so.

On the other hand, the group of cases of obstruction of the splenic and portal veins without cirrhosis of the liver show conspicuous splenomegaly. This has been generally regarded as the result of the stimulation of the cytoplasmic reticulum of the red pulp. It is commonly referred to as congestive splenomegaly. Moschcowitz [9] has recently pointed out that the stimulus of chronic hypertension of the portal circulation is the decisive factor in the structural transformation which the spleen undergoes in this situation. Our results show a striking diminution in percentage of white pulp, although the absolute weight remains unchanged. In other words, the increase in size is due almost exclusively to red pulp growth, the white pulp remaining untouched by the process.

The fact that the percentage of trabeculae remains relatively constant, indicating that the trabecular system keeps pace with the splenic enlargement, may reflect the response of the organ to prolonged venous hypertension or stasis. Most other forms of splenomegaly do not show this. On the other hand, the diseases of this group are usually of longer duration than the others, and it may be that trabecular growth is a slow process and bears a direct relation to the duration of the splenic enlargement.

A corollary of these results is that the reticulum apparently retains its capacity to form trabecular fibers. One might speculate that the trabecular system is continually undergoing destruction and replacement of its fibrous tissue, analogous to the changes which are thought to occur in bone.

It is not clear why similar changes should not occur in chronic cardiac failure. It can only be pointed out that there are important

9. Moschcowitz, E.: The Pathogenesis of the Splenomegaly in Hypertension of the Portal Circuit (Congestive Splenomegaly), to be published.

differences between the central (cardiac) and peripheral (portal system) types of hypertension and stasis of the splenic venous system—i. e., the presence of collateral circulation in the cases of disease of the splenic or the portal vein, and the presumed differences in the height, the duration and the intermittency of the venous pressure.

Cirrhosis.—The white pulp, although probably significantly decreased, shows much less change in percentage in splenomegaly accompanying cirrhosis than in the purely obstructive splenomegalies. In fact, the absolute weight is twice normal. This suggests strongly that the portal obstruction in Laennec's cirrhosis is not the only factor responsible for the splenomegaly. Something has stimulated the white pulp as well as the red, although not to as great a degree.

The results in cirrhosis with obstruction of veins show a higher percentage of trabeculae, in keeping with the purely mechanical factor of back pressure. If the splenomegaly were due exclusively to portal hypertension, one would expect little difference in these groups. The conclusion is probably warranted that the spleen plays more than a passive role in cirrhosis. Furthermore, the hyperplasia of white pulp favors the hypothesis that an additional factor (perhaps inflammatory) is concerned.

One of the original hypotheses of this investigation was that if the spleen were studied in a large enough group of cirrhoses, some factors might emerge which would permit a subdivision of this relatively heterogeneous group of diseases in terms of the behavior of the spleen; i. e., that an analysis of the nature of the splenomegaly might lead to a better understanding of the different stages and subdivisions of the cirrhoses. For example—it is probable that splenic enlargement occurs in Laennec's cirrhosis prior to the development of portal hypertension. Would a comparison of this type of spleen and one representing an advanced case of the disease reveal any important differences? Unfortunately, the number of cases available for study was insufficient to permit such an analysis.

Infectious Disease—Subacute Bacterial Endocarditis.—It has been noted [8] that the malpighian corpuscles are often very large in this condition. We have been able to confirm that there is a decided growth of the lymphatic tissue. The figure of 8.5 per cent for the white pulp is the highest of all the results for the abnormal spleens. In pathogenetic terms, both the white and the red pulp appear to be implicated in this disease. The increase of white pulp is very likely a reflection of the role of the lymphatic tissue in the formation of antibody. One could speculate that the lymphatic percentage should be even higher in cases in which subacute bacterial endocarditis has reached the bacteria-free stage, in which presumably the body has developed a high resistance

to the invading organism. In the single case in which we were able to make measurements, however, this was not true (weight of spleen, 800 Gm.; trabeculae, 1.99 per cent ± 0.69; white pulp, 3.38 per cent ± 1:39; red pulp, 94.63 per cent).

In subacute bacterial endocarditis the trabeculae are decreased—presumably because of the relatively rapid evolution of the splenomegaly.

FINAL SUMMARY

A method is described for the quantitative estimation of the percentages of red pulp, white pulp and trabeculae of the spleen. The results for 30 "normal" spleens are compared with those obtained in 71 cases of splenomegaly classified pathogenetically. The different components are found to grow in different proportions in the various diseases. From these results certain inferences are drawn regarding the mechanism of splenic enlargement and the nature of the disease processes investigated.

VIRAL VERSUS TOXIC HEPATIC NECROSIS

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THAT acute hepatitis may be due to a hepatotoxic virus has been demonstrated by epidemiologic investigations and studies on human volunteers.[1] The fatal and the benign form of this condition were previously called acute yellow atrophy and catarrhal jaundice, respectively. Epidemiologic considerations were primarily responsible for the acceptance of a viral causation of the different forms of hepatitis encountered in the armed forces of almost all nations engaged in World War II. However, the question arises whether in the civilian population most instances of a similar clinical picture of primary (benign or fatal) acute hepatitis without known epidemiologic background are of the same, presumably viral, causation. One method of approach to the solution of this problem is a pathologic analysis of the cases of primary fatal hepatic necrosis (commonly called hepatitis) observed in a large civilian general hospital during the past eighteen years and a comparison of the morphologic picture with that of similar cases observed in military personnel. All instances in which the hepatic damage was a complication of another disease causing death were omitted from this study. Excellent studies[2] from the Army Institute of Pathology on the fatal form of this acute hepatic necrosis (epidemic hepatitis) in military personnel serve as the basis for such a comparison. The question of the causation of primary hepatitis in civilians is significant from the diagnostic, the prognostic and the therapeutic standpoint.

The literature on this point is not too clear. Epidemic outbreaks of hepatitis occurring in wartime, especially in military personnel, have

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1. (*a*) Neefe, J. R.: M. Clin. North America **30**:1407, 1946. (*b*) Havens, W. P., Jr.: J.A.M.A. **134**:653, 1947. (*c*) Oliphant, J. W., in Harvey Lectures, Baltimore, Williams & Wilkins Company, 1943, vol. 39, p. 254.

2. (*a*) Lucké, F.: Am. J. Path. **20**:471, 1944. (*b*) Lucké, B., and Mallory T.: ibid. **22**:867, 1946.

been known for a good many years.[2a] Epidemics of this disease occurring in the civilian population in peacetime have been repeatedly reported from various countries.[3] It was only after a series of outbreaks in the second World War that the viral causation of epidemic hepatitis was fully accepted.[4] Previously, bacteria, especially those of the enteric group, had been considered the infectious etiologic agents by many.[5] The viral causation of epidemic hepatitis was indicated not by actual culture but by successful transmission to human volunteers of a material which is temperature resistant and is not destroyed by low concentrations of disinfectant.[1] In contrast to the naturally occurring hepatitis, transmitted by the gastrointestinal route, the form known as homologous serum jaundice is due to the parenteral administration of infected blood products via blood and plasma transfusion, vaccinations and use of improperly sterilized syringes.[6] The naturally occurring infectious hepatitis seems to differ immunologically from, and has a much shorter incubation period than, homologous serum jaundice.

After the exclusion of obvious cases of toxic hepatitis due to known hepatotoxic agents, the question arises whether the remaining instances of sporadic hepatitis are all viral in origin. Some investigators are willing to make this assumption,[7] while others [8] consider epidemic and sporadic catarrhal jaundice different diseases. Eppinger's [9] monograph

3. (*a*) Frohlich, C.: Deutsches Arch. f. klin. Med. **24**:394, 1879. (*b*) Cockayne, E. A.: Quart. J. Med. **6**:1, 1912. (*c*) Symmers, D.: J.A.M.A. **74**:1153, 1920. (*d*) Jones, C. M., and Minot, G.: Boston M. & S. J. **189**:531, 1923. (*e*) Blumer, G.: J.A.M.A. **81**:353, 1923. (*f*) Chomet, B.: Med. Klin. **30**:1428, 1934. (*g*) Bohrmann, U. F.: Ergebn. d. inn. Med. u. Kinderh. **58**:201, 1940. (*h*) Hardy, L. H., and Feemster, R.: New England J. Med. **235**:147, 1946. (*i*) Wallgren, A.: Acta paediat. **9** (supp. 2):1, 1930. (*j*) Wickstrom, J.: ibid. **28**:385, 1940. (*k*) Alsted, G.: Am. J. M. Sc. **213**:257, 1947. (*l*) Bergstrand, H.: Ueber die akute und chronische gelbe Leber Atrophie, Leipzig, G. Thieme, 1930.

4. (*a*) Cameron, J. D. S.: Quart. J. Med. **12**:139, 1943. (*b*) MacCallum, F. O.: Brit. M. Bull. **1**:112, 1943. (*c*) Demadarin, K., and Harfall, J. T.: Brit. M. J. **2**:587, 1944. (*d*) Gezon, H. M.: U. S. Nav. M. Bull. **43**:579, 1944. (*e*) Barker, M. H.; Capps, R. B., and Allen, F. W.: J.A.M.A. **128**:997, 1945. (*f*) Gutzeit, K.: München. med. Wchnschr. **89**:161, 1942. (*g*) Dietrich, S.: Deutsche med. Wchnschr. **68**:5, 1942. (*h*) Holler, F.: ibid. **68**:724, 1942.

5. (*a*) Ottenberg, R., and Spiegel, R.: Medicine **22**:27, 1943. (*b*) Lichtman, S. S.: Diseases of the Liver, Gall Bladder and Bile Ducts, Philadelphia, Lea & Febiger, 1942.

6. Morgan, H. V., and Williamson, D. A. J.: Brit. M. J. **1**:750, 1943. Beeson, P. D.: J.A.M.A. **121**:1332, 1943. Findley, G. M.; Martin, N. H., and Mitchell, J. B.: Lancet **2**:301 and 365, 1944. Sawyer, W. A.; Meyer, K. F.; Eaton, M. D.; Bauer, J. H.; Putnam, P., and Schwentker, F. F.: Am. J. Hyg. **39**:337, 1944; **40**:35, 1944. Bigger, J. W.: Lancet **1**:457, 1943. Neefe.[1a] Havens.[1b]

7. Bohrmann.[2g] Wallgren.[2i]

8. Selander, P.: Acta paediat. **23** (supp. 4):1, 1939.

9. Eppinger, H.: Die Leberkrankheiten, Berlin, Julius Springer, 1937.

fails to mention the epidemic nature of catarrhal jaundice, and one of his co-workers [10] even attempted to disprove the possibility of its infectious causation. An early attempt at differentiating between epidemic catarrhal jaundice and other forms of contagious and noncontagious jaundice was made [11] but was difficult due to lack of etiologic knowledge.

The histologic picture of primary hepatitis has been thoroughly studied. The picture of the benign form as first described by Eppinger [9] was based on the study of livers of soldiers suffering from this disease who had died a traumatic death. He concluded that catarrhal jaundice is the nonfatal form of acute atrophy of the liver and called the disease parenchymal hepatitis. His findings were confirmed by the study of biopsy and necropsy specimens.[12] In recent years the widely expanded use of the hepatic biopsy has permitted a thorough study of the pathologic aspects of the nonfatal type.[13]

Fatal hepatic necrosis is a subject of extensive description in the textbooks of pathology, not always, however, with clear differentiation of the different forms. The recent wave of fatal epidemic hepatitis is reflected in a large series of anatomic descriptions of the disease from military personnel [14] and civilians.[15] The most thorough studies have been performed by Lucké and Mallory,[2] at the Army Institute of Pathology. There are ample descriptions of the hepatic necrosis occurring in man as a result of the action of known toxins [16]—for instance,

10. Lainer, F.: Wien. klin. Wchnschr. **53**:601, 1940.

11. Wilcox, W. H.: Brit. M. J. **1**:565, 605 and 639, 1919.

12. Wessel, C.: Acta path. et microbiol. Scandinav. **58**:533, 1924. Nordmann, O.: Med. Klin. **21**:1746, 1925. Klemperer, P.; Killian, J. A., and Heyd, C. G.: Arch. Path. **2**:631, 1926. Schrumpf, A.: Ann. d'anat. path. **9**:17, 1932. Gaskell, J. F.: J. Path. & Bact. **36**:257, 1933. Barber, H., and Osborn, G. R.: ibid. **49**:581, 1934. Popper, H.: Wien. klin. Wchnschr. **49**:207, 1936.

13. (*a*) Iversen, P., and Roholm, K.: Acta med. Scandinav. **102**:1, 1939. (*b*) Roholm, K., and Iversen, P.: Acta path. et microbiol. Scandinav. **16**:427, 1939. (*c*) Dible, J. H.; McMichael, J., and Sherlock, S. P. V.: Lancet **2**:402, 1943. (*d*) Axenfeld, H., and Brass, K.: Frankfurt. Ztschr. f. Path. **57**:147, 1942; **58**:220, 1944; **59**:281, 1948. (*e*) Mallory, T. B.: J. A. M. A. **134**:655, 1947. (*f*) Rappaport, E., and Klatskin, G.: Rev. Gastroenterol. **14**:17, 1947.

14. Wood, D. A.: Arch. Path. **41**:345, 1946. Siegmund, H.: Virchows Arch. f. path. Anat. **311**:180, 1944. Berk, J. E.: Gastroenterology **8**:296, 1947. Stokes, J. F., and Miller, A. A.: Quart. J. Med. **16**:211, 1947. Cameron.[4a]

15. Taylor, H. E.: Am. J. Clin. Path. **17**:314, 1947. Fox, J. P.; Manso, C.; Penna, H. A., and Madureira, P.: Am. J. Hyg. **36**:68, 1942. Nicod, J. L.: Gastroenterologia **71**:62, 1946. Roulet, F.: Virchows Arch. f. path. Anat. **310**:436, 1943. Wood, D. A., and Black, M. B.: Am. J. Clin. Path. **16**:746, 1946.

16. Hanser, R.: Atrophie, Nekrose, Ablagerungen und Speicherungen (sog. Degenerationen), in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol. 5, pt. 1.

carbon tetrachloride,[17] chloroform,[18] phosphorus,[19] mushroom poison [20] and the toxins developing after severe burns.[21] In the older literature, however, emphasis had already been focused on the difference between the hepatic necrosis due to known poisons, such as phosphorus, and the so-called yellow atrophy of unknown cause. [22]

MATERIAL AND METHOD

The material of this study includes 136 patients with fatal primary hepatic necrosis who came to autopsy at the Cook County Hospital during the period of 1929 through 1947. The total number of autopsies in this period was 23,028. As already mentioned, only those patients were included who had jaundice and in whom hepatic insufficiency was the cause of death. Clinically they were considered as having hepatitis. Their hepatitis was not a complication of another disease which was in the foreground of the picture. Anatomically, these cases of disease of the liver have been recorded as cases of acute or subacute atrophy of the liver or as cases of fatal hepatitis. Cases of acute damage of the liver in cirrhosis were not incorporated. It was often difficult to draw a line between cirrhosis and chronic hepatitis. In general, cases in which there was far advanced distorted reconstruction of the lobular pattern of the liver were excluded. The instances of fatal chronic hepatitis included actually represent examples of the larger group of postnecrotic cirrhosis. Histologic material was available in 95 cases, and in some of these the gross specimens could be studied.

The material from military personnel used for comparison was obtained from two Army hospitals which served during the war as histopathologic centers. It is not consecutive in character and permits, therefore, no statistical evaluation as to incidence.

The liver tissue was in most instances fixed in 10 per cent formaldehyde solution U.S.P. Occasionally, material preserved in acetic acid-Zenker solution, formaldehyde-Zenker solution or in Carnoy solution was available. In all cases, sections stained with hematoxylin and eosin were studied. They were usually supplemented with sections stained with Mallory's aniline blue and Gömöri's or the Foot-Bielschowsky reticulum fiber stain.

RESULTS OF STUDIES ON MATERIAL FROM MILITARY PERSONNEL

The livers of 15 among 18 soldiers dying of primary hepatic necrosis presented a morphologic picture similar to that of fatal epidemic hepatitis as described by Lucké and Mallory.[2] These cases were classified as a "viral" group.

I. VIRAL GROUP

In this group, in which the viral causation is strongly suggested by the epidemiologic background of Army life and exposure, examples

17. Peery, T. M.: Arch. Path. **26**:923, 1941.
18. Fischler, F.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:553, 1913.
19. LaDue, T. S.; Schenken, J. R., and Kuker, L. H.: Am. J. M. Sc. **208**:223, 1944.
20. Klemperer, P.: Virchows Arch. f. path. Anat. **237**:400, 1922.
21. Hartman, F. W., and Romence, H. L.: Ann. Surg. **118**:402, 1943.
22. Paltauf, R.: Verhandl. d. deutsch. path. Gesellsch. **5**:91, 1902. Klemperer.[20]

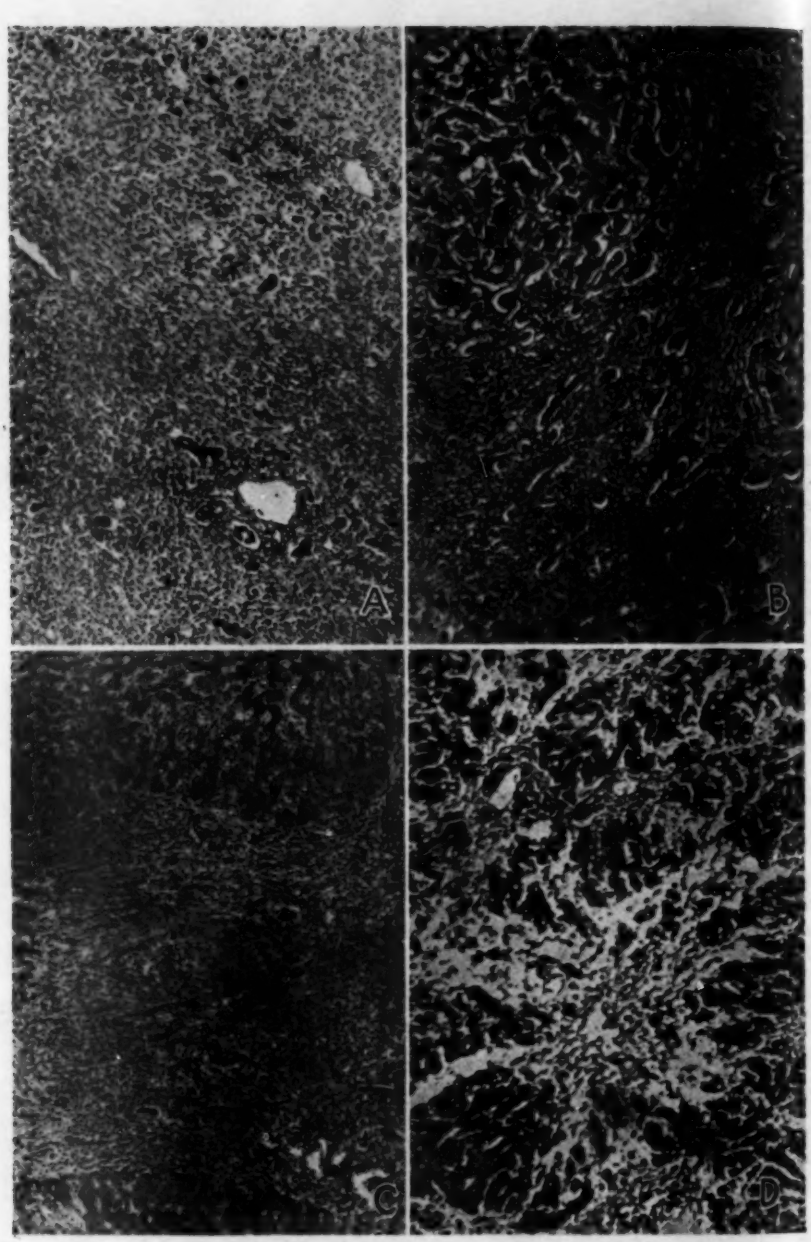

Fig. 1.—*A*, fulminant form of viral necrosis with almost complete disappearance of liver cells, in a soldier. In the meshes of the denuded framework are phagocytic mononuclear cells; such cells accumulate also in the periportal field.

B, subacute form of viral necrosis in a soldier. In the greater part of the section the connective tissue framework is denuded of liver cell cords and replaced by mononuclear exudate cells and a few regenerating liver cell cords resembling bile ducts. In addition, nodules composed of liver cell cords, not arranged around a central vein, are seen.

C, chronic viral necrosis in a soldier. Irregularly arranged nodules which have resulted from distorted reconstruction are separated by wide bands in which many mononuclear cells and liver cell cords resembling bile ducts are found.

D, central toxic necrosis in a soldier. The central half of the nodule is denuded of liver cells. In the meshes of the collapsed framework are a few exudate and Kupffer cells. The periportal fields are free of exudate cells.

of the acute fulminating (fig. 1 *A*), subacute (fig. 1 *B*) and chronic (fig. 1 *C*) forms were found, as summarized in table 1. The clinical histories of the patients, the laboratory findings and the gross and histologic pictures follow the classic description of Lucké and Mallory.[2] A detailed analysis would be repetitious. In the acute form, rapid disintegration of the liver cells and marked mesenchymal reaction are in the foreground.

In most of the studied cases the destruction was acute in character, with little evidence of regeneration. The hepatitis was fulminant in accordance with the nomenclature of the Army Institute of Pathology. As expected, in military material, the third decade of life, the male sex and the white race are predominant. In more than half of the cases there were recognized possible etiologic factors, such as plasma or

TABLE 1.—*Studied Military Cases of Fatal Hepatic Necrosis*

Stage or Form	Cases	Average Days Since Outbreak of Jaundice	Average Age	Sex: Male	Sex: Female	Race: White	Race: Negro	Etiologic Factors
Cases of "Viral" Type								
Stage:								
Fulminant	9	5.9	26.9	9	0	8	1	Blood transfusions 3 Plasma transfusions 2
Subacute	5	28.0	31.8	4	1	4	1	Arsenical injections 1 War injuries 2
Chronic	1	165.0	21.0	1	0	0	1	Unknown 7
Totals	15		28.1	14	1	12	3	Known 8 Unknown 7
Cases of "Toxic" Type								
Form:								
Central necrosis	3	9	30	3	0	2	1	Bout of acute alcoholism 1

blood transfusions. In 1 instance, intravenous injections of arsenical compounds was recorded, and from the time elapsed between the injection and the appearance of jaundice, a diagnosis of homologous serum hepatitis was possible.

II. TOXIC GROUP

Among the studied cases of fatal hepatitis in Army personnel, 3 did not conform with the given description of viral hepatitis, although clinically they were also characterized by hepatic insufficiency and morphologically by far reaching destruction of the parenchyma of the liver. One case is presented as an example:

A 44 year old white soldier had had an attack of jaundice thirty years before death while he was in Central America. Ten years later he had malaria. About ten years before he was last admitted to the hospital he received 106 injections of arsenical and bismuth compounds for syphilis. He also stated that he had drunk ½ to 1 pint (about 300 cc.) of whisky daily for the past twenty years. Twenty-four

hours after a bout of heavy drinking, he acquired a fever of 102.4 F., and had pain in the right upper quadrant of the abdomen and diarrhea and started vomiting. He became moderately jaundiced, and the liver was palpable 3 fingerbreadths below the costal margin. The spleen was not palpable. There was tenderness in the right subcostal region. The urine contained bilirubin, a trace of sugar and albumin but no leucine or tyrosine crystals. The red blood cell count was 4,400,000; the hemoglobin content, 90 per cent. The white blood cell count was 9,800, of which 80 per cent were polymorphonuclears, 18 per cent lymphocytes and 2 per cent monocytes. The icterus index was 80; the immediate direct van den Bergh reaction was positive; the serum nonprotein nitrogen was 160 mg. per hundred cubic centimeters; the serum albumin was 4.2 Gm. and the serum globulin 3.7 Gm. per hundred cubic centimeters. The jaundice gradually deepened, and slowly anuria developed. The patient died eight days after the onset of the jaundice in uremia.

At autopsy the liver weighed 1,860 Gm. Its surface was moist and the capsule thickened. The organ was slightly firmer than normal. The cut surface was brownish yellow and mottled with small depressed areas. Microscopically (fig. 1A), in the central and intermediate zone of the lobules the connective tissue framework appeared collapsed and almost denuded of liver cells. The reticulum fibers as such were not interrupted. The Kupffer cells were moderately proliferated and laden with biliary material. Few histiocytic phagocytes were present. Red cells accumulated in and around the sinusoids. In the border zone of these areas, remnants of liver cells were seen without nuclear staining. They were eosinophilic and revealed shadows of the cellular structure. Around them were large cell fragments of similar appearance. There were almost no inflammatory changes. The liver cells in the periphery of the lobules appeared intact and contained small and large fat droplets. The cords were separated from the wall of the sinusoids by edema fluid. The periportal fields were small and devoid of cellular reaction. A few inflammatory cells were found in the walls of the central veins.

Comment.—In age and sex distribution these 3 cases are identical with those of the previous group (table 1). The interval of time between the outbreak of jaundice and death is apparently longer in this than in the fulminant viral group, although the series is too small for a definite conclusion. Histologically, the lesion is definitely zonal, and in the 3 examined cases restricted to the central portion of the lobule. The liver cells in the peripheral part appear intact. However, they are swollen and surrounded by edema fluid. On the border between the intact and the necrotic area a gradual transition is noted in that the liver cells may reveal small fat droplets or small or large, bright red, strongly refractile, irregularly shaped clumps as a result of coagulation necrosis. They are often arranged around the nucleus and show a tendency to coalesce. Finally, the nuclei do not stain and may disintegrate, and in the central areas large remnants and fragments of liver cells are observed. Most of them are anuclear, but the cellular structure is still present in a ghostlike fashion, even though part of the cytoplasm appears coagulated. Small phagocytosed cell fragments are rare. The reticular framework is intact but collapsed, and in its meshes, in addition to the liver cell fragments, a few exudate cells, some of

them polymorphonuclear in type, may be seen. There are few exudate cells in the periportal field, and cords of regenerating liver cells are not conspicuous. Bile duct proliferation is almost entirely absent.

COMPARISON OF THE TWO GROUPS

The first group discussed, which appears identical with the cases described by Lucké and Mallory,[2] is assumed to be cases of the so-called infectious or epidemic hepatitis. The etiologic agents in this group are, according to our present knowledge, the viruses responsible for epidemic and homologous serum hepatitis. This "viral" group is characterized by rapid disintegration of liver cells with formation of chiefly small cell fragments hardly recognized in routine stains, denudation of the framework with marked mesenchymal cellular reaction and phagocytosis, involvement of the entire lobule and cords of regenerating liver cells which simulate bile ducts in the lobular periphery.

The second form is characterized by predominantly zonal involvement, with gradual death of the liver cells. The diseased cells reveal fatty metamorphosis and coagulation necrosis. However, the cell remnants or large cell fragments in which the nuclei are not stained any longer or have disintegrated still permit recognition of cellular structure (ghost cells). The framework is denuded without marked inflammatory reaction, and few regenerative changes are noted. In 1 instance in this group an acute alcoholic bout was elicited as the etiologic factor.

The morphologic differences between the first and the second group lead to the assumption of a different causation and, therefore, also a different designation for the second group. Only in 1 instance was an actual hepatotoxic etiologic factor elicited. Nevertheless, the morphologic picture is similar to that seen in patients as a result of the action of known hepatotoxic poisons, such as carbon tetrachloride, or that of the central necrosis so well described by F. B. Mallory [23] many years ago, which is found as a common complication although usually not as a cause of death in many conditions in which toxic factors, such as bacterial, endogenous or exogenous poisons, are established. Since the difference between such pictures and the one in our cases of this group is a matter of degree, the designation "toxic necrosis" or "toxic hepatitis" appears justified. A similar nomenclature had already been applied to such cases several years ago.[24]

RESULTS OF STUDIES OF MATERIAL FROM CIVILIANS

Over the period studied (1929 to 1947) the 136 cases of primary fatal necrosis of the liver represent an average of 0.59 per cent of the entire autopsy material. Although in recent years this percentage

23. Mallory, F. B.: J. M. Research **6**:264, 1901.
24. Kirschbaum, J. D., and Popper, H.: Arch. Int. Med. **65**:465, 1940.

has been somewhat exceeded,[25] yet in general the distribution over the years remained fairly constant (fig. 2). In this material 47 per cent of the patients were male and 53 per cent female; 58 per cent were white and 42 per cent Negro; the age ranged from 3 weeks to 78 years. A possible etiologic factor was recorded in almost one third of the cases (table 2). Most often mentioned was administration of arsenical compounds; next came acute alcoholic bout and pregnancy. Furthermore, in the material studied there were a number of accompanying conditions (table 3) which, although not the cause, may have had a modifying influence on the changes in the liver.

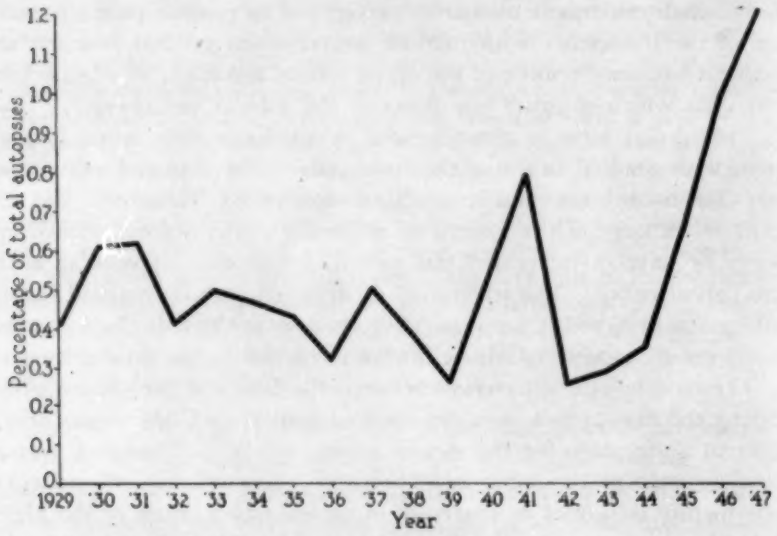

Fig. 2.—Yearly incidence of acute fatal hepatic necrosis in autopsies at Cook County Hospital, Chicago.

MORPHOLOGIC EXAMINATION

The morphologic criteria used in military personnel for differentiating between a viral and a toxic group were applied to the 95 civilian cases in which histologic material was available. In 26 of them the picture resembled that seen in the cases classified as viral in the Army material, whereas the remaining 69 cases were tentatively classified as instances of toxic hepatitis.

I. VIRAL GROUP

Following the classification used with the military material, the cases of the viral type were subdivided into those of a fulminant, those

25. Reference deleted by the authors.

TABLE 2.—*Possible Etiologic Factors in 136 Cases of Fatal Acute Hepatic Necrosis*

Etiologic Factors	Cases	Percentage of Total
Administration of arsenical compounds	10	7.4
Blood transfusions	7	5.18
Acute alcoholism	4	2.96
Pregnancy	4	2.96
Administration of mercurial compounds	3	2.24
Administration of sulfonamide compounds	3	2.24
Contact with patients having catarrhal jaundice	2	1.48
Administration of barbiturates	2	1.48
Administration of cinchophen	1	0.74
Lead	1	0.74
Attempted suicide with "creolin"	1	0.74
Turpentine	1	0.74
Salmonella paratyphi	1	0.74
Total	40	29.8

TABLE 3.—*Conditions Accompanying Fatal Acute Hepatic Necrosis in 136 Cases*

	Cases
Syphilis	14
Tuberculosis	8
Chronic alcoholism	7
Diabetes mellitus	2
Malnutrition and avitaminosis	3
Trauma	3
Arthritis	1
Scarlet fever	1
Staphylococcus infection	1
Epilepsy	1
Pregnancy (complicating arsenical hepatitis)	1
Thrombopenic purpura	1
Total	38

TABLE 4.—*Studied Civilian Cases of Fatal Hepatic Necrosis*

Stage or Form	Cases	Average Days Since Outbreak of Jaundice	Average Age	Sex: Male	Sex: Female	Race: White	Race: Negro	Etiologic Factors	
Cases of "Viral" Type									
Stage:									
Fulminant	12	6.1	34.3	5	7	7	5	Blood transfusions	4
Subacute	9	23.5	35.7	3	6	6	4	Injection of arsenical compounds	2
Chronic	5	42.0	41.7	3	2	2	4	Contact with "catarrhal" jaundice	1
Totals	26		36.2	11	15	15	11	Known	7
								Unknown	19
Cases of "Toxic" Type									
Form:									
Central necrosis	44	10.4	43.0	20	24	25	19	Administration of:	
								Mercurial compounds	1
								"Creolin"	1
								Trinitrotoluene	1
Fatty necrosis	15	8.5	40.1	6	9	8	7	Arsenical compounds	2
								Barbiturates	2
Peripheral necrosis	3	17.5	38.0	1	2	2	1	Carbon tetrachloride	2
Transition into post-necrotic cirrhosis	7	39.2	46.2	4	3	5	2	Sulfonamide compounds	2
								Alcoholism	2
Total	69		42.5	31	38	40	29	Known	28
								Unknown	56

of a subacute and those of a chronic stage (table 4), for each of which an example is presented.

Fulminant "Viral" Hepatitis.—The patient was a 20 year old Negro girl whose medical and surgical history was essentially negative and whose menstrual history was normal. Four days before she was admitted to the hospital, moderately severe intermittent epigastric pain developed, radiating to her back. The following day a local physician noticed jaundice and advised that she rest in bed. She became increasingly drowsy and comatose. On admission her temperature was 101.8 F. Hepatic dulness was absent on percussion over the right lower two ribs anteriorly. There was bilateral sustained ankle clonus. The urine contained some albumin and considerable bilirubin. The blood dextrose was 41 mg. per hundred cubic centimeters; the carbon dioxide–combining power, 22 per cent by volume; the serum nonprotein nitrogen was 61 mg. and creatinine 2.2 mg. per hundred cubic centimeters; the icteric index was 60. Despite intravenous administration of dextrose, saline solution, plasma, Ringer's solution, lactated, U.S.P., and penicillin, she grew steady worse and died fifteen hours after admission.

At autopsy the flabby, brownish red liver weighed 1,090 Gm. The wrinkled capsule was thin and smooth; in the cut surface lobular markings were not made out in the greater part of the organ, which here revealed a deep red color. Only in circumscribed foci were the markings recognized, the acinous centers being dark red and the peripheral areas light yellow. Histologically (fig. 3A), the connective tissue framework was completely denuded of liver cells except for a small rim on the periphery of the lobule. The intermediate and peripheral zone showed an extremely dense infiltration with round-cellular elements, many of them macrophages. The central areas showed only a moderate infiltration of these elements. Their abundant cytoplasm was often laden with bile-stained material and occasionally contained a few small fat droplets. Between them small, diffusely eosinophilic cell fragments were seen in large number. A few of the liver cells revealed diffuse coagulation necrosis with loss of nuclear staining and cellular detail; they resembled Councilman bodies because of their hyaline, refractile appearance. The Kupffer cells were proliferated, phagocytic and hardly differentiated from the macrophages. Lymphocytes, plasma cells and eosinophils were seen in moderate amount. Neutrophilic granulocytes were almost absent. In the periphery of the lobules many regenerating liver cells in short cords, often revealing fatty changes, were found. The dilated bile capillaries frequently contained exudate cells or bile thrombi. The shape of the nuclei differentiated the cords from proliferated bile ducts.

Subacute "Viral" Hepatitis.—A 13 year old Negro girl was perfectly well until three months prior to being admitted to the hospital, when intermittent epigastric pain and severe headaches developed. One month later she became icteric and her urine turned dark. Two weeks later her abdomen swelled and edema of the ankles and feet developed. She felt weak and was dyspneic on exertion. She became disoriented and began to vomit. Her temperature was 100 F. She had hyperactive reflexes; the liver, the spleen and the lymph nodes were not palpable. The otherwise normal urine contained bile. The red and white blood cell counts were normal; the serum nonprotein nitrogent was 25 mg. per hundred cubic centimeters; the total serum protein was 6.7 Gm. per hundred cubic centimeters; the prothrombin time was normal; the cephalin-cholesterol flocculation was 3 plus; the spinal fluid was normal. She died on the seventh hospital day in cholemia.

At autopsy, the greenish brown liver weighed 850 Gm., and its capsule was smooth. The surface revealed reddish irregular mottling, especially marked over the right lobe. The consistency was markedly diminished. The brownish green cut

surface showed reddish mottling throughout, with the acinous centers being made out only in places. Quite often were seen yellow nodules, up to 4 mm. in diameter, which showed no lobular pattern. The microscopic picture (fig. 3B) revealed great polymorphism. In some areas the connective tissue framework of the lobules was collapsed, with almost complete disappearance of the liver cells. The vascular pattern, however, was well preserved, and some irregularly proliferating strands

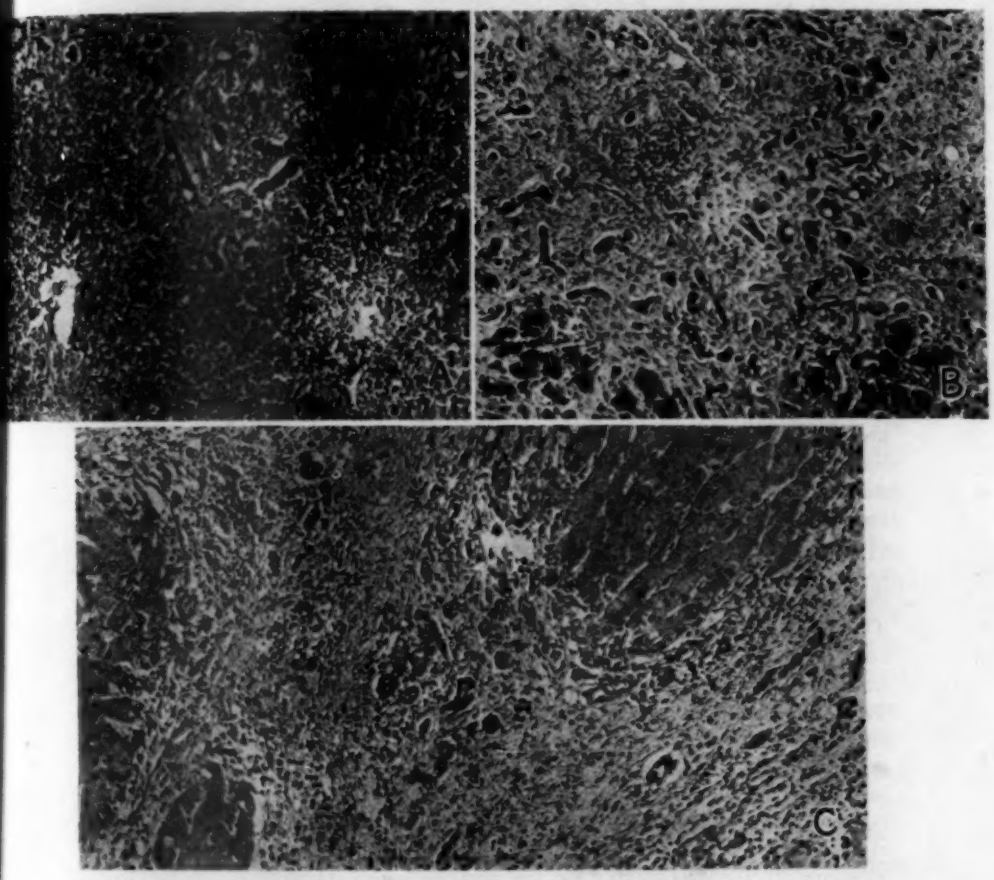

Fig. 3.—*A*, fulminant form of viral necrosis in a civilian. In the meshes of the denuded connective tissue framework are many red cells and phagocytic mononuclear cells. The latter also infiltrate densely the portal triads. A few irregular cords of regenerating liver cells may be noted.

B, subacute form of viral necrosis in a civilian. Areas of collapsed connective tissue reveal mononuclear exudate cells and irregularly regenerating liver cell cords. These surround small nodules composed of liver cell cords without normal lobular pattern.

C, chronic form of viral necrosis (postnecrotic cirrhosis) in a civilian. Irregularly arranged pseudolobules are surrounded by wide bands of collapsed framework in which there are round exudate cells and regenerating liver cell cords resembling septal bile ducts.

of liver cell cords were noted. They often showed formation of multiple files of liver cell cords and dilated central bile capillaries. Between the cords were many round phagocytic exudate cells; hardly any liver cell fragments were seen. The dilated sinusoids, engorged with red cells, were often of almost angiomatous character. In a few areas, however, normal liver cell cords were seen, partially arranged in regenerated nodules without characteristic pattern. In the centers of the lobules and nodules the liver cells were atrophic and often laden with bile pigment. No mesenchymal reaction was present. The portal triads revealed moderate round cell infiltration.

Chronic Viral Hepatitis.—A 30 year old Negro woman was well until three months prior to being admitted to the hospital, then sharp midback and abdominal pains, swelling of the hands and feet and progressive jaundice gradually developed. Episodes of nausea and vomiting, as well an increasing dyspnea, appeared later. Her symptoms gradually increased in severity. Her temperature on admission was 99 F. and her pulse rate 112. The liver and the spleen were not palpable. The urine contained considerable bile pigment but no urobilinogen. The hemoglobin content was 66 per cent; the red, white and differential blood cell counts were normal; the icterus index was 95. Despite parenteral administration of blood, fluids and vitamins, she became increasingly lethargic and died in coma.

The liver weighed 500 Gm. and was deformed. The capsule was thin and in places wrinkled. The consistency varied; the color was deep greenish red. The right lobe contained a large node, which on section consisted of greenish yellow protruding liver tissue with indistinct markings. It was surrounded by dark red tissue sinking below the cut surface in which lobular markings were fairly well made out. Circumscribed, irregularly outlined scars, free of liver tissue, contained regularly spaced vessels. Histologically (fig. 2C), the connective tissue framework of many lobules was in circumscribed areas almost completely denuded of liver cells and collapsed. However, the original vascular pattern was preserved, with the portal triads and central veins being much closer to each other than usual. The reticulum framework was not thickened or collagenized and was easily differentiated from the thick connective tissue of the portal triads. In the meshes of the framework some scattered slender cords of regenerated liver cells were noted. These simulated proliferated bile ducts but contained dilated bile capillaries and bile casts. They were surrounded by many larger and smaller phagocytic exudate cells. The portal triads themselves showed little bile duct proliferation. Round cell infiltration in and around lymphatic channels was noted. In other areas liver cell nodules predominated, which apparently were regenerated and not arranged around central veins. The nodules varied in size and were irregularly spaced. Their structure otherwise resembled the few areas in which the original lobular pattern was preserved. In both lobules and nodules central atrophy and degeneration of liver cells were occasionally seen in addition to irregularly scattered focal necroses. Areas of marked bile inhibition of Kupffer and liver cells indicated focal disturbances of bile drainage. Evidence pointing toward a protracted course of the disease were: (1) preformed liver lobules with signs that blood and bile flow had met interference; (2) collapsed areas in which destruction and inflammatory response were still present; (3) reconstructed areas.

Comment.—In general, the cases of acute hepatic necrosis in civilians selected for this group show a histologic picture which is more or less identical with that noted in the viral group in the military material.

Morphologically, the basic phenomenon is the rapid destruction of the liver cells, which in these fatal cases is rather diffuse, with some centrolobular accentuation. Gradual cell death is not found and, as Lucké [28] pointed out, fatty changes and coagulation necrosis are not essential parts of the picture. Large remnants or fragments of cells in which the cellular structure appears preserved, but nuclear staining is absent, are as a rule not seen. A large number of small cellular fragments, however, can be noted between the mesenchymal cells, especially in the earlier stages of the process. This becomes more conspicuous on the use of special technics, such as fluorescence microscopy.[26] Only rarely, in the early stages of the fulminant form, are large eosinophilic liver cell fragments seen which reveal coagulation necrosis and also some fatty metamorphosis, but, as a rule, no imbibition of bile pigment. These fragments seem, however, to disintegrate rather rapidly, and the cell structure is hardly made out. Occasionally in the acute stages, bright red, refractile, mostly round elements occur which represent diffusely hyalinized liver cells, simulating the Councilman bodies found in yellow fever. They are separated from the liver cell cords, may be surrounded by mononuclear cells and are considered characteristic for the nonfatal form of viral hepatitis.[13e] Most of the cell fragments are phagocytosed by macrophages and proliferated and mobilized Kupffer cells. Mesenchymal macrophages in the interstitial tissue may simulate degenerated shrunken liver cells which are laden with bile pigment. In general, phagocytosis is an important part of the picture. The absence of liver cells in wide areas in which, especially in the fulminant form, the framework is denuded, is not easily recognized under low power microscopic examination, which reveals a very cellular tissue. However, as Lucké [28] emphasized, the cells are mostly histiocytic and macrophagic elements, chiefly of round cell type (fig. 4*A*). In addition, plasma cells and lymphocytes are not uncommon. Neutrophilic polymorphonuclear leukocytes are in the background. Eosinophilic cells are sometimes prominent. A similar infiltration mostly by round cellular exudate cells is found in the portal triads, chiefly arranged around lymphatic channels. Many of the histiocytes contain pigments. Almost no fatty metamorphosis is seen except for occasional small fat droplets accumulated in some isolated regenerating cells. The cellular infiltration may be less marked in older cases. In the earlier stages regeneration takes place mostly in the form of liver cell cords, which may become wide and bizarre in character. Regenerating hepatic cell cords often simulate proliferating bile ducts but may be differentiated by the character of their nuclei and the presence of bile capillaries in the center.

The gross appearance of the liver also agrees with the description published by Lucké and Mallory.[2] In some of the instances of the

26. Volk, B. W., and Popper, H.: To be published.

fulminant type and in the more acute stages of the subacute type, the cut surface is diffusely dark red and sunken in and the lobular markings are absent in almost the entire liver. This appearance, caused by the disappearance of the liver cells and the collapse of the framework, simulates a hyperplastic spleen (fig. 5 *A*). More often, however, in the entire liver or in smaller or larger confluent or irregularly outlined fields which are yellow or green and prominent, the markings are distinct or even exaggerated. In addition to variations in the disappearance of liver cells, the blood content varies. The predominance of blood over cell cords, which usually is more outspoken in the central part of the lobule, produces the gross impression of passive congestion

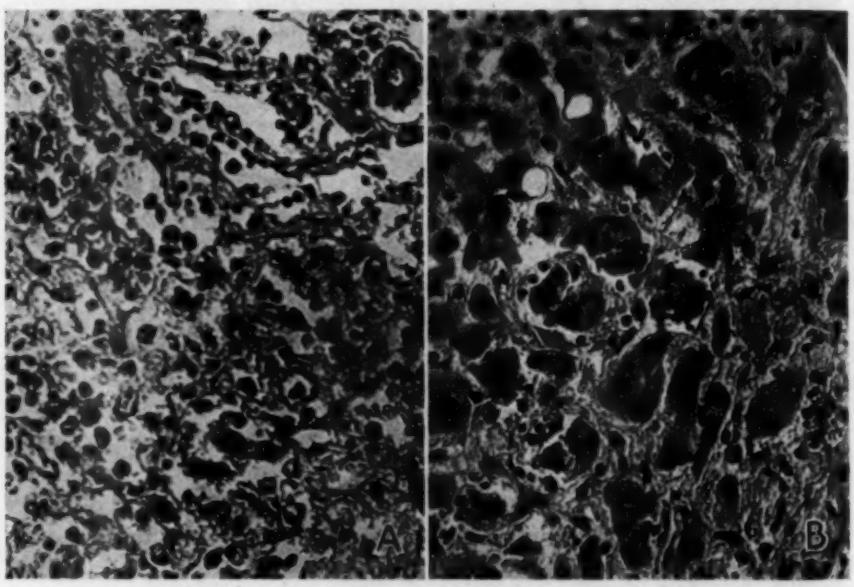

Fig. 4.—*A*, high power field of fulminant viral necrosis. No liver cells are seen. The picture is dominated by bile-laden macrophages and proliferated Kupffer cells. Between them are a few diffusely hyalinized round refractile liver cells and small hardly recognizable cell fragments. The portal triad which is indicated by a small bile duct also reveals cellular infiltration.

B, high power field of the border zone of acute central toxic necrosis. The liver cells reveal coalescing clumps of coagulated protein and some fat vacuoles. Other cells without nuclear staining reveal shadows of cellular structure, as do large liver cell fragments. Kupffer cell mobilization, but little infiltration of exudate cells, is present.

and even of an exaggerated nutmeg liver (Lucké [2a]). There are usually great differences between the various portions of the liver, especially between the right and the left lobe (fig. 5 *B*). This variegated picture is even more outspoken on the cut surface. It is produced by different degrees of damage of the liver cells; moreover, the process seems to be of different age in different portions of the liver. In general,

the liver is flabby and collapses when placed on the autopsy table. In the subacute form of the disease, nodular foci of regeneration of different size and color give the cut section a variegated appearance, and the consistency usually does not differ much from the normal. To differentiate the chronic form from the toxic [27] or postnecrotic [28] cirrhosis is obviously difficult in view of the gradual transition from one to the other. Because of this, the selection of the material often had to be

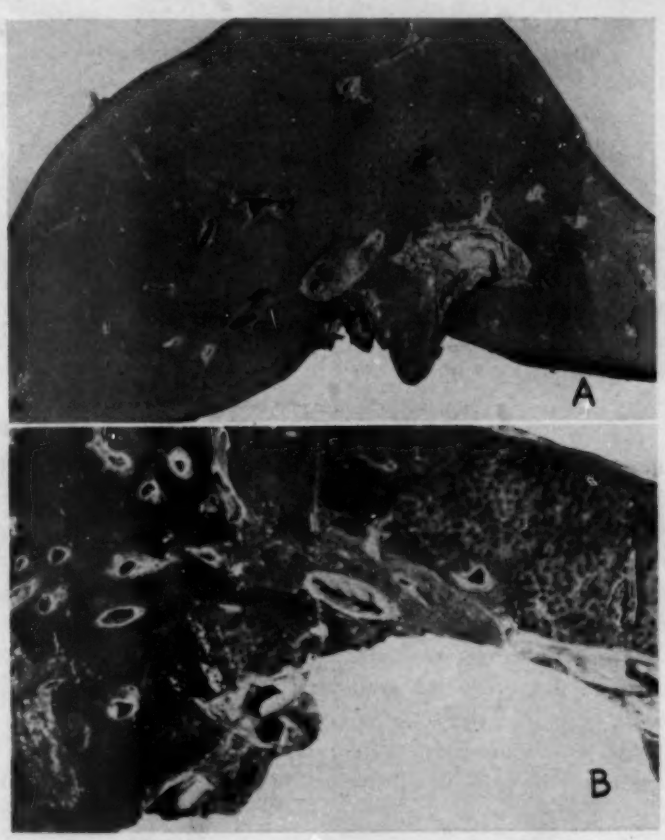

Fig. 5.—*A*, gross specimen of liver in case of acute viral necrosis. The lobular markings are entirely missing, and a spleenlike appearance is presented.
B, gross specimen showing acute viral necrosis with marked difference between various portions of the liver. Some areas have a spleenlike appearance with loss of lobular markings, whereas in other circumscribed areas (especially in the left lobe), the lobular markings are exaggerated.

arbitrary. The origin from hepatitis with necrosis of whole lobules is indicated by grossly visible scarlike bands consisting of collapsed liver

27. Mallory, F. B.: New England J. Med. **206**:1231, 1932.
28. Karsner, H. T.: Am. J. Clin. Path. **13**:569, 1943.

tissue in which the closely approximated vessels are clearly apparent. Only cases in which extensive areas of the liver revealed evidence of still active viral hepatitis were included. This explains the relatively small number of cases in this group.

The average number of days between outbreak of jaundice and death is similar to that in the Army group (table 4). The age group is slightly higher, which is characteristic for the studied hospital population. In contrast to Army material, the female sex predominates. Color incidence is almost equally distributed in this group, though roughly one third of the patients admitted to the hospital were Negroes. The etiologic factors of civilian hepatitis compare with those noted in the military group. They were, however, less often elicited in view of the less accurate epidemiologic history. Moreover, in previous years exposure to blood derivatives may not have been recorded, since its significance was not known.

We can thus conclude that in civilians a picture may appear which is identical histologically with the viral hepatitis found in military personnel, and we may, therefore, be justified in considering this group as also viral in origin.

II. TOXIC GROUP

As already mentioned, in 65 civilian cases of primary fatal hepatic necrosis, the histologic picture differed from that of the previously described cases in the viral group. In the majority of these civilian cases the histologic appearance simulated those of the 3 soldiers who were placed in the toxic group with central necrosis. In addition, there were cases in which the liver reveaed peripheral necrosis or predominant fatty changes. Furthermore, there were instances of chronic liver cell damage which also revealed transition into a postnecrotic cirrhosis; however, in these cases the destructive process was still acute or recurrent and followed the toxic rather than the viral pattern. Again a few cases were selected, more or less as examples of a larger group, because in them the acute destructive process was still very much in the foreground. An example of each of these four groups follows:

Acute Toxic Hepatitis with Central Necrosis.—A 42 year old white man attempted suicide by swallowing approximately 4 ounces (118 cc.) of carbon tetrachloride. He was admitted to the hospital in stuporous condition, vomiting considerable amounts of blood-tinged material. After emergency treatment consisting of gastric lavage, sedation and parenteral feeding, the patient was well until the third hospital day. Then he began to have jaundice and tenderness in the right upper quadrant of the abdomen. The following day oliguria became evident. The urine revealed at this time albumin (3 plus), bilirubin (4 plus), urobilinogen (4 plus) and an occasional red blood cell and granular cast. The serum nonprotein nitrogen was 56 mg. per hundred cubic centimeters; cephalin-cholesterol flocculation was 4 plus; thymol turbidity was 10.2 units; alkaline phosphatase was 12 Bodansky units;

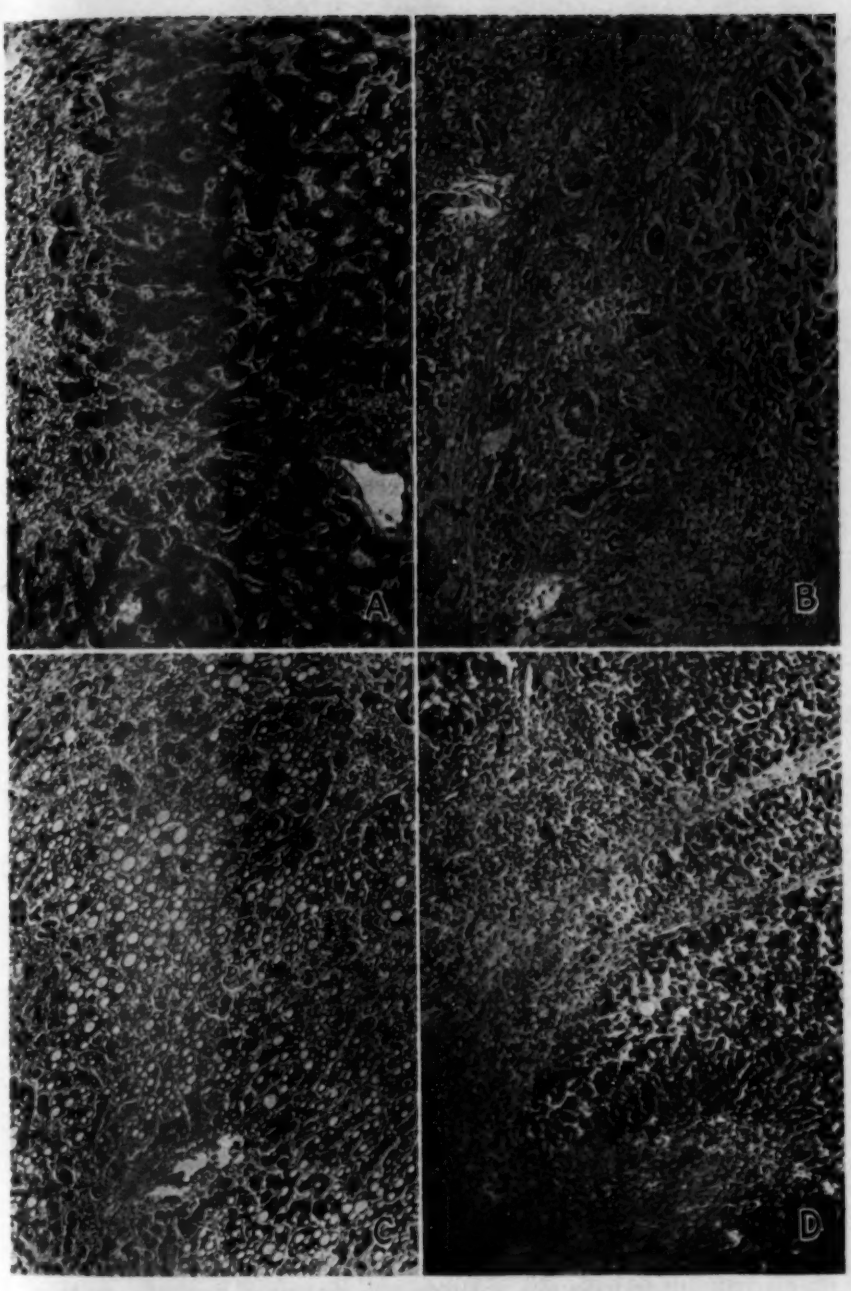

Fig. 6.—*A*, central toxic necrosis in a civilian. In the central half of the lobule, the liver cell cords are missing, and in the meshes of the collapsed connective tissue are large organized liver cell remnants and fragments without nuclear staining. There is little concentration of exudate cells in the necrotic area and the portal triads. Marked edema is noted in the intact portion of the lobule.

B, peripheral toxic necrosis in a civilian. The liver cells in the peripheral zone of the lobule have disintegrated, but large anuclear liver cell fragments are found. In the intact border zone there is dissociation of the liver cell cords.

C, fatty toxic necrosis in a civilian. Diffuse fatty metamorphosis is seen; in the central portion of the lobule the liver cells disintegrate. Here large liver cell fragments are noted without significant numbers of exudate cells.

D, chronic toxic necrosis (postnecrotic cirrhosis) in a civilian. In the wide bands separating irregularly arranged pseudolobules, moderate cellular infiltration, chiefly lymphocytes, is noted. Phagocytic elements and liver cell regenerates resembling proliferating bile ducts are absent.

the total serum protein was 6.8 Gm. per hundred cubic centimeters, and the icteric index was 64. His jaundice deepened, and he became anuric and died on the eighth hospital day, in coma. On the day prior to death the serum nonprotein nitrogen was 158 mg. per hundred cubic centimeters and the icterus index was 118.

At autopsy the liver was deeply yellow tinged, had diminished consistency and weighed 1,750 Gm. The edge was blunt and the capsule tense. The lobular pattern on cut section seemed exaggerated by marked congestion in the central areas. Histologically (fig. 6A), the liver cell cords in the central and intermediate zone were barely recognizable. Many of the liver cells had disappeared; the remaining cells failed to reveal nuclear staining, but otherwise structural details were recognized. Their cytoplasm often revealed small or large fat droplets; in addition, it contained irregularly shaped, strongly eosinophilic clumps. It was usually diffusely pigmented with bile. Also many cell fragments of similar character were noted. The Kupffer cells were proliferated and contained phagocytosed material. The sinusoids were, as a rule, wide, and occasionally fibrin thrombi were seen in them. Bile-laden inflammatory monocytes were sparsely intermixed. Only peripherally in the lobules were the liver cells fairly well preserved. The perisinusoidal spaces were widened. The portal triads revealed a few round-cellular and polymorphonuclear exudate cells.

Acute Toxic Hepatitis with Peripheral Necrosis.—A Negro woman aged 43, a factory worker, who had malaria at the age of 13, underwent, three weeks prior to being admitted to the hospital, nausea, vomiting and epigastric distress. One week later she became jaundiced, had acholic stools and dark urine. Eight months prior to this hospitalization she had three "hip shots," the nature of which was unknown. The physical examination gave essentially negative results. The icterus index was 312; the serum nonprotein nitrogen was 33 mg., the chlorides 375 mg., and the total cholesterol 208 mg. per hundred cubic centimeters; the cholesterol ester ratio was 35 per cent; the serum albumin was 3.3 Gm. and the globulin 3.0 Gm. per one hundred cubic centimeters. The urine revealed albumin (a trace), bilirubin (4 plus), no urobilinogen and an occasional white blood cell. The red blood cell count was 4,500,000 and the white cell count 13,450. Roentgenologically, a calcific density on the right side opposite the second lumbar vertebra was interpreted as "possible gallbladder or common duct stone." On the sixth hospital day, choledochostomy was performed and a rubber drain inserted. The gallbladder appeared collapsed, and a small stone was found in the fundus. The common bile duct was not dilated. The patient had hemorrhages from the mouth and from the operative wound. She gradually became worse and died on the sixteenth hospital day.

At autopsy the flabby liver weighed 770 Gm. The capsule was gray and slightly wrinkled. The cut surface was brownish red. The lobular pattern was generally obscured, and only in circumscribed areas did it appear more marked than usual. Microscopically (fig. 6*B*), in the central portion of the lobule, dissociation of otherwise intact liver cell cords and edema were noted. In the peripheral zone, however, the connective tissue framework was completely denuded of liver cells, producing the impression of enlarged portal triads. In the denuded areas, a few bile-laden liver cells with or without nuclear staining were noted. Many exudate cells, chiefly polymorphonuclear leukocytes, were seen in and around the lymphatic channels of the periportal fields. The bile ducts showed moderate proliferation. The areas around the central veins were normal.

Acute Fatty Hepatitis.—A 53 year old white laborer who had been epileptic for several years fell and struck his head on the ground during an epileptiform attack. The scalp wound was not serious; however, the next day he noticed a yellow

color of the skin and scleras. He became increasingly drowsy and stuporous and was admitted three days after his injury in a semicomatose condition with a temperature of 102.6 F., a pulse rate of 128, a respiratory rate of 24, moderate jaundice and rales in the lower lobe of the right lung. The liver was palpable 3 finger-breadths below the costal margin; the spleen was not palpable. The urine revealed bilirubin (4 plus), no urobilinogen, albumin (3 plus), and occasional red and white blood cells. The icterus index was 71. The patient's stuporous condition gradually increased, and he died on the third hospital day. Despite thorough search, no evidence of intoxication of any sort was found.

At autopsy the large, dark green liver weighed 2,700 Gm.; its consistency was doughy, but soft. The edges were rounded and the capsule tense. On the greasy cut surface the markings were visible, the lobules being peripherally yellow green, with reddish centers.

Histologically (fig. 6*C*), small and large fat droplets replaced the cytoplasm of the liver cells diffusely. Liver cells with at least partially nonfatty cytoplasm were seen only on the lobular periphery. Throughout, but more marked in the central zone, the liver cells contained bile-stained granules and ramified perinuclear eosinophilic clumps. The sinusoids were narrow, and, especially in the central zone, scarcely any red cells were found. In the central zone the liver cells were disintegrated, and bile-stained remnants and large fragments without nuclear staining were irregularly scattered. They revealed fatty changes and clumps of coagulated protein and were surrounded by only few, if any, exudate cells, mostly of round-cellular character. The latter possibly derived from the large proliferating Kupffer cells, which contained brown-stained coagulated or fatty material in almost all parts of the lobule. There were few exudate cells in the portal triads, chiefly of polymorphonuclear character. The bile ducts revealed no changes.

Chronic Toxic Hepatitis.—A rash, jaundice and headaches developed in a 36 year old white woman after she had worked for eleven months with trinitrotoluene in a naval ordnance plant. Three other workers in the plant in whom similar symptoms developed died. In six months she had apparently recovered. She was well for four months, and then she began to complain of menorrhagia. This and gradually increasing weakness and dyspnea were her only complaints until three months later, when a generalized rash developed with epistaxis and bleeding from the gums. On admission she was markedly anemic and revealed petechiae all over the body. The mucous membranes of the mouth and gums showed evidence of bleeding. Liver, spleen and lymph nodes were palpable. The urine showed albumin (2 plus) and many red blood cells. The red blood cell count was 1,020,000, with 26.8 per cent reticulocytes; the hemoglobin content was 15 per cent; the white cell count was 4,500, with a normal differential count; the platelets were almost completely absent. After several blood transfusions, splenectomy was performed, but the patient died immediately after the operation.

At autopsy the liver weighed 1,300 Gm. and was greenish brown, with coarse, irregular granulations. Large nodules were separated by firm connective tissue bands of variable widths in which lumens of vessels were often present. In the nodules, which measured up to 2 cm. in diameter, the lobular markings were well recognized. Microscopically (fig. 6*D*), in the greater part of the liver the original lobular pattern appeared distorted by enlargement of the portal triads, the lymphatic channels of which were infiltrated with round and polymorphonuclear cells. In some areas, the lobular pattern was absent, and regenerated pseudolobules or nodules predominated. These likewise revealed little alteration of the liver cells themselves. Between the lobules and nodules were wide areas almost devoid of liver cells; only few necrotic cells and irregularly scattered anuclear cell fragments were found in

the collapsed connective tissue framework. There was almost no proliferation of fibers. Between them, occasionally polymorphonuclears or round exudate cells were found, which were mostly small and not phagocytic. Proliferated bile ducts were seen in the portal triads and the larger scars. They were clearly differentiated from regenerating liver cell cords by their small dark nuclei and the absence of bile casts. These areas of collapse without any sign of reconstruction were obviously the residue of preceding extensive necrotizing processes which had completely destroyed several lobules.

Comment.—The common histologic abnormalities in all 69 cases of this group are zonal necrosis and the silent denudation of the connective tissue framework. Relatively little response of mesenchymal cells, if any, is seen around the disintegrating liver cells. If present, it is at least partially and sometimes predominantly polymorphonuclear in character. The latter character is especially marked where the liver cells are still arranged in intact cords. The exudate cells reveal little phagocytosis. The Kupffer cells, however, are mobilized, and they contain phagocytosed breakdown products of liver cells. The liver cells themselves demonstrate various degrees of degeneration and disintegration. Their cytoplasm loses the normal basophilia and is eosinophilic; small and large fat droplets appear, especially in the fatty form of the disease; in addition smaller and larger clumps of strongly refractile coagulated protein are seen in the cytoplasm, usually arranged around the nucleus. They may coalesce to form larger ramified bodies resembling the hyaline material described by F. B. Mallory [29] in alcoholic cirrhosis. Complete coagulation necrosis of entire liver cells is seldom found. Around the coagulated clumps hydropic degeneration may be noted. In the immediate vicinity of the necrotic area the nuclei of the liver cells lose their basophilic staining or less often become pyknotic or break up. Remnants of liver cells are found which still reveal the structural organization of the liver cells but are uniformly eosinophilic or may reveal diffuse imbibition of bile pigment (ghost cells) (fig. 4 *B*). They break up into irregularly outlined large eosinophilic or bile-pigmented fragments in which, also, the previous structure is still suggested, indicating a slow cell death. Round, diffusely hyalinized bodies of the character of Councilman bodies were not seen in the cases examined. Regenerative processes, if any, are in the background and, when present, do not reveal a bizarre or "wild" character. Mitoses, however, are more common than they are normally, especially on the borderline of the necrotic portion. The sinusoids often contain recently formed fibrin thrombi, especially in the necrotic areas. There is marked widening of the perisinusoidal spaces, which contain albuminoid debris. Edema is outspoken in all forms but the fatty hepatitis. It is present not only in the necrotic areas, where the framework is often separated by

29. Mallory, F. B.: Bull. Johns Hopkins Hosp. **22**:69, 1911.

fluid, but also in the histologically intact zone. The portal triads are hardly involved except in the peripheral or the chronic form, the cellular infiltration often including polymorphonuclear cells. The zonal arrangement is far more outspoken than in the viral form. In the fatty variety it is concealed by the diffuse fatty metamorphosis.

In the toxic group the centrolobular necrosis is the most common picture (table 4), representing a more advanced stage of the well known

Fig. 7.—*A*, gross specimen showing acute toxic fatty necrosis. The lobular markings are obscured on the uniform-appearing cut surface.
B, gross specimen showing acute toxic central necrosis. On the cut surface the lobular markings are exaggerated.

phenomenon observed at autopsy in many toxic conditions. It is followed in incidence by the fatty change, which comprises less than a fourth of the cases. In the fatty form the fatty metamorphosis is usually diffuse throughout the lobule; however, the necrotic changes which differentiate this form from simple fatty degeneration or infiltration are mostly centrolobular. Peripheral necrosis was only rarely encountered.

Necrosis of the intermediate zone was not seen in the series examined. The small number of instances of chronic hepatitis in this series is explained by the difficult and arbitrary separation from postnecrotic cirrhosis.

In the gross the liver in the acute type of fatal toxic hepatic necrosis is relatively large and usually reveals a blunt edge. The lobular markings are in many instances obscured because of the edema or because of the relatively low blood content in the fatty form (fig. 7 *A*). In other instances, especialy in the presence of central necrosis (fig. 7 *B*), the increased blood content in the collapsed central areas exaggerates the lobular pattern. In small circumscribed areas the hyperemic and collapsed central fields are connected by bridges surrounding the small remnants of intact parenchyma in the periphery of the lobules. The

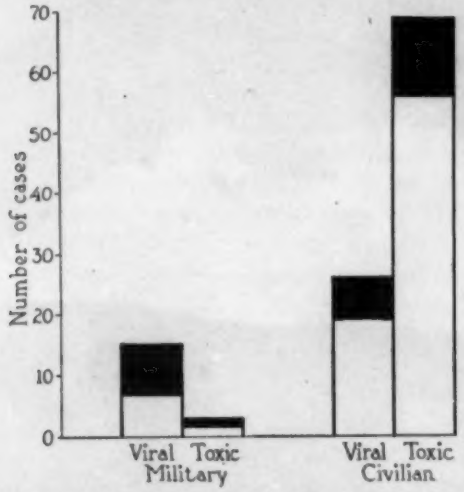

Fig. 8.—Incidence of viral and toxic fatal hepatic necrosis in the studied military and civilian material. Solid black portions represent cases of known cause; white portions, cases of unknown cause.

picture then appears rather similar to subacute passive congestion of the liver. It is differentiated from it by the rather low consistency. Even in the fatty form, despite its doughy character, the consistency is diminished. The picture of the entire liver, especially on the cut surface, is rather uniform and little difference between the lobes is apparent. The disease process appears to be of equal age in the entire liver. The gross picture of the peripheral form does not vary much from that of the central one. The fatty form obviously reveals a greasy appearance.

All cases showed clinically evidence of hepatic failure and more or less severe jaundice. In only 13 of the 69 cases were etiologic factors, usually considered hepatotoxic, recorded. The average number of days between outbreak of jaundice and death was somewhat greater in the

acute central form than in the fulminant viral form; in the fatty form it was almost as short. The few cases of the peripheral form revealed a longer duration. The average age was higher in the toxic than in the viral group; sex and color distribution were not characteristic.

TABLE 5.—*Histologic Characteristics That Differentiate Between "Viral" and "Toxic" Hepatic Necrosis*

	"Viral" Type	"Toxic" Type
Distribution of damage	Diffuse, with central predominance	Usually zonal
Cell death	Rapid	Gradual
Large cell remnants or fragments without nuclear staining but with shadows of cellular structure (ghost cells), often with diffuse imbibition of bile	Absent, except for rapidly disintegrating cells in very early fulminant form	Present
Cytoplasmatic clumps of coagulated protein	Usually absent	Often marked
Hyalinization of cells due to diffuse coagulation necrosis (Councilman bodies)	Present	Absent
Fatty changes	Little, if any (small droplets)	May be marked (small and large droplets)
Denudation of connective tissue framework	Reactive	Silent
Rupture of framework	Absent	Occasionally present
Edema with widening of perisinusoidal space	Absent	Outspoken except in fatty form
Cellular infiltration	Chiefly mononuclears	Less marked; polymorphonuclears may predominate
Bile-containing macrophages	Many	Few
Phagocytosis	Marked	Moderate or slight
Fibrin thrombi	Rare	Rather common
Liver cell regeneration in form of pseudo bile duct proliferation	Common	Often absent

TABLE 6.—*Gross Characteristics That Differentiate Between "Viral" and "Toxic" Hepatic Necrosis*

	"Viral" Type	"Toxic" Type
Size of liver	Usually reduced	Slightly enlarged in central necrotic form, moderately to markedly enlarged in fatty form
Uniformity of picture	Often absent	Present
Cut surface	Spleenlike or focally exaggerated lobular pattern	Diffusely obscured or exaggerated lobular pattern
Consistency	Markedly reduced	Slightly reduced
Greasy appearance	Absent	Occasionally present

COMPARISON OF THE TWO GROUPS

A comparison of the viral and the toxic group in the civilian material permits conclusions similar to those drawn in regard to the military group. The far greater number of cases studied makes the observations more valid. In the civilian material studied there is, quite unexpectedly, a definite preponderance of the histologic picture considered as toxic necrosis over that considered as viral in origin (fig. 8).

The histologic differences between the two groups have been considered previously. Table 5 represents an attempt to summarize them. The histologic differentiation in individual cases was only occasionally difficult.

Grossly, the distinction between the toxic and the viral group was not always easy; the characteristics used are summarized in table 6. In general, the liver with the viral form of hepatitis reveals a more variegated outer and cut surface than that with the toxic form, in which the variations between the different parts of the liver are far less marked and the lobular pattern in the acute form is uniform throughout. The consistency is reduced in both groups but always more in the viral hepatitis which reveals the characteristic picture of acute yellow atrophy.

TABLE 7.—*Weight of Liver and Spleen in Viral and Toxic Hepatic Necrosis*

Stage or Form	Cases in Which Weight of Liver Was Known	Weight of Liver in Gm.		Cases in Which Weight of Spleen Was Known	Weight of Spleen in Gm.	
		Average	Range		Average	Range
		Cases of "Viral" Type				
Stage:						
Acute	16	1,284	990-1,750	9	286	200-500
Subacute	11	1,076	780-1,575	8	198	90-375
Chronic	7	1,176	800-1,500	3	215	180-250
Totals	34	1,194	800-1,750	20	245	90-500
		Cases of "Toxic" Type				
Form:						
Central necrosis	24	1,560	800-3,280	16	247	90-650
Fatty necrosis	13	2,340	1,400-4,100	11	241	60-300
Peripheral necrosis	2	1,450	700-2,140	2	190	175-250
Chronic	8	1,795	1,200-2,250	7	207	120-360
Totals	47	1,810	770-4,100	36	234	60-650

The liver is on the average larger in the toxic form than in the viral form. It weighs, especially in the fatty variety of the toxic form, more than normal, in contrast to the reduced weight of the liver in the viral form (table 7). This enlargement, which is indicated by the blunting of the edges, is to a great degree caused by the marked edema which characterizes the toxic form.[24] Fat deposition, blood engorgement and preservation of liver cells in part of the lobule are other factors responsible for the relatively large size of the liver in toxic necrosis.

The spleen may be enlarged in both groups, showing the picture of a reactive hyperplasia in the acute and subacute form and that of a fibrocongestive splenomegaly in the chronic one. No characteristic differences between viral and toxic necrosis are found.

As to changes in the abdominal lymph nodes, the available records are incomplete. In the viral group observed during the performance of this study the hyperplasia described by Lucké[28] was noted. This was less evident in the toxic group.

The kidneys reveal cholemic nephrosis with the characteristic bile casts in cortex and medulla and the degenerative changes of the tubules far more often in the toxic than in the viral form. Oliguria and even anuria may develop; in many instances of toxic necrosis, as in carbon tetrachloride poisoning, full-fledged low nephron nephrosis is observed.[30] In the fulminating viral form, fat droplets are found in the tubular cells of the cortex as described by Lucké and Mallory [2b]; this, however, is not associated with impaired renal function or oliguria. The difference in the renal involvement between fatal toxic and viral necrosis is reflected in the generally much higher rise in the serum nonprotein nitrogen in the toxic as compared with the viral form (table 8). The differences between the viral and the toxic form in the morphologic picture of the kidney and the elevation of the nonprotein nitrogen are especially marked in the acute and less clear in the chronic stage.

TABLE 8.—*Serum Nonprotein Nitrogen in the Studied Fatal Cases of Hepatic Necrosis*

Type	Cases in Which Nonprotein Nitrogen Was Recorded	Nonprotein Nitrogen in Mg. per 100 Cc. of Serum	
		Average	Range
"Viral"	15	42.1	17-75
"Toxic"	25	88.7	20-232

III. COMBINATION OF VIRAL AND TOXIC CHANGES

In several instances in which the liver had the appearance of subacute or chronic viral necrosis, the centers of the regenerated nodules or of the preformed lobules revealed acute necrosis characteristic of the toxic type, namely, gradual disintegration of liver cells without significant mesenchymal reaction. An example of this is shown in the following case of homologous serum hepatitis.

A 71 year old white man was operated on for carcinoma of the colon, at which time he received several blood transfusions. Two months later he noticed a yellow discoloration of his skin and a dark color of his urine; his stools became clay colored. He complained of abdominal cramps, distention and anorexia. He stayed at home under a local physician's care for a week, but his condition did not improve and he was admitted to the hospital. Except for the moderate jaundice, the physical examination gave essentially negative results. The urine contained bilirubin (3 plus) and urobilinogen (1 plus). The red cell count was 3,000,000, with hemoglobin content 72 per cent; the white blood cell count and the differential count were essentially normal. His temperature rose to 101.2 F.; he gradually became stuporous and died in a coma on his seventh hospital day.

At autopsy the liver weighed 780 Gm. and was slightly softened. The irregular surface was in general yellowish red and revealed many small nodules of variable

30. Lucké, B.: Mil. Surgeon **99**:371, 1946.

size (from 0.3 to 1 cm. in diameter), some of which were brown. The cut surface showed loss of the lobular structure. The small nodules were separated by gray trabeculae. Microscopically (fig. 9*A*), the connective tissue was collapsed in wide areas. The arrangement of the vessels, however, was preserved. Many irregularly regenerating liver cell cords, which contained bile casts in the dilated bile capillaries, were seen in the collapsed areas. The shape of these cells was usually bizarre. In the framework were also noted histiocytes and lymphocytes, both accumulating chiefly in the periportal fields. Liver cell fragments were almost absent. Irregularly scattered throughout the organ were small islets of well formed liver cells. Most of them were reconstructed pseudolobules without the cords arranged around the central vein, and only in a few places did they reveal a normal lobular structure. Both the nodules and the preformed lobules showed a circumscribed central zone

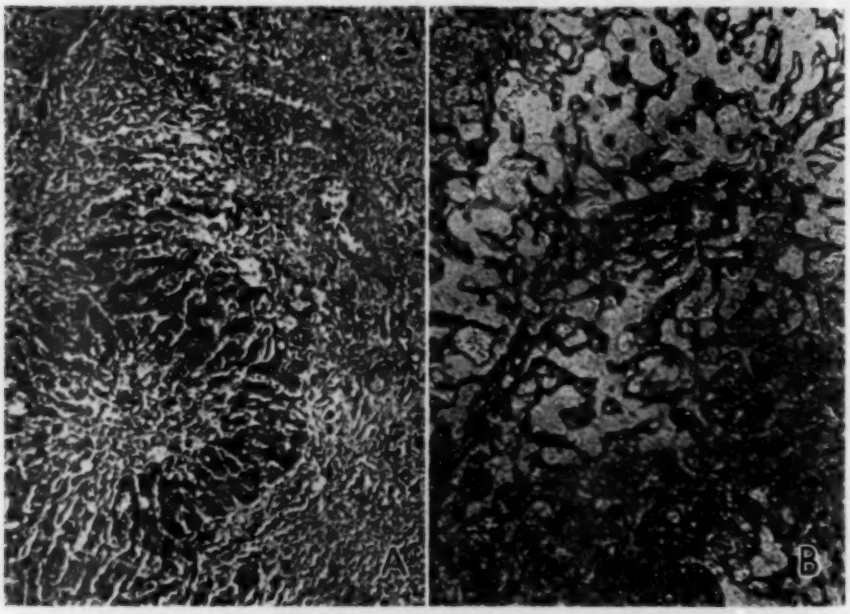

Fig. 9.—*A*, subacute viral necrosis with "toxic" necrosis in the center of a nodule. A collapsed framework containing irregular regenerating liver cell cords and mononuclear exudate cells surrounds the liver nodule. In its center there is denudation of the framework, associated with little cellular exudation but with presence of large liver cell remnants which still reveal the shadows of cellular structure.

B, central toxic necrosis with rupture of the reticulum framework (Gömöri's reticulum fiber stain). In circumscribed areas the fibers are widely separated and ruptured. This produces large blood pools.

in which the liver cells were either not present or revealed lack of nuclear staining with shadows of the cellular structure and imbibition of bile. They contained coagulated clumps of protein. Large liver cell fragments of similar character were also present. Edema and collapse of the framework were seen. However, cellular infiltration was missing, and only the Kupffer cells were proliferated. This transition between the necrobiotic and the intact areas was gradual.

Comment.—The recent central necroses occurring quite commonly in the preformed lobules or the regenerated nodules were probably the ultimate cause of death since they had destroyed part of the remaining functioning parenchyma which still had been able to maintain life. The morphologic picture speaks against a viral causation of the recent parenchymal damage but suggests the effect of toxic substances injuring an already damaged liver, and one can thus speak of secondary toxic necrosis. However, these toxic lesions are similar to those seen in passive congestion of the liver,[31] which are obviously caused by anoxia of tissues resulting from retardation of the blood flow. Recently [32] the possibility has been emphasized that central hepatic necrosis may be the result of circulatory disturbances, and especially the centrolobular necrosis in the fatty form has been explained by the obstructing of the sinusoidal blood flow by the swollen liver cells. Likewise, the centrolobular necrosis in the more chronic forms of viral necrosis may possibly be due to a retardation of the blood flowing through the sinusoids in the central part of the lobule or the nodule. This could be explained by the distortion of the vascular bed in these cirrhotic or precirrhotic conditions.[33] For blood to flow normally through all parts of all lobules of the liver it is required that the distance between tributaries of the portal veins and the central veins be identical all over the liver.[34] This structural principle is destroyed by irregular nodule formation. If in such a condition some minor cause interferes only slightly with the general hepatic circulation, the centers of lobules and nodules may become necrotic if the hepatic circulation was a priori disturbed by the distortion of the lobular pattern in chronic hepatitis. The central anoxic necrosis, often fatal in subacute viral hepatitis, is, therefore, not necessarily explained by persistent activity of the virus or an additional injurious substance, but is possibly caused by anoxia and can thus be a sequela of the original disease.

IV. CONNECTIVE TISSUE FRAMEWORK

The intralobular reticulum framework is intact in all forms of viral hepatitis, as clearly shown by Lucké.[35] Even where complete denudation and collapse of the framework occurred, the fibers revealed neither rupture nor evidence of proliferation. In the material of the toxic group, also, the framework appeared intact except for the case to be presented now.

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31. Mallory, F. B.: J. M. Research **24**:455, 1911.
32. Himsworth, H. P.: The Liver and Its Diseases, Cambridge, Mass., Harvard University Press, 1947.
33. McIndoe, A. H.: Arch. Path. **5**:23, 1928.
34. Pfuhl, W., in Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1932, vol. 6, pt. 2.
35. Lucké, B.: Am. J. Path. **20**:595, 1944.

A 57 year old white man was admitted to the hospital with progressive abdominal swelling of six months' duration. Two months prior to admission he had acquired a nonproductive cough and began to notice an icteric tint to his skin. At that time he also felt some abdominal discomfort, especially marked in the right upper quadrant. His past history was essentially irrelative. On examination moderate jaundice, ascites, and tenderness in the right upper quadrant of the abdomen were noted. The liver and the spleen were not palpable. The urine contained bilirubin (2 plus). The hemoglobin content was 82 per cent; the red cell count, 4,200,000 and the white cell count 11,150, with a normal differential picture; the serum nonprotein nitrogen was 38 mg. and the total cholesterol 156 mg. per hundred cubic centimeters, with an ester ratio of 54.5 per cent; the alkaline phosphatase was 11.2 Bodansky units, and the icterus index was 90 units. Roentgenologic examination of the chest and the gastrointestinal tract revealed no abnormality. The patient declined rapidly, dying on the fifteenth hospital day.

At autopsy the liver was brown and weighed 1,510 Gm. It was of firm consistency and revealed a granular surface and a smooth capsule. On the cut surface the lobular markings were obscured, and an irregular fine red mottling was noted. Around some central veins a wide dark red area was found. The portal triads appeared widened. Microscopically (fig. 9*B*), the structure of the liver cell cords in the centers of the lobules was distorted. Individual liver cells were dissociated and were diffusely bile stained; occasionally, their cytoplasm contained refractile eosinophilic inclusions of ramified shape. In addition, some large anuclear cell fragments were present. Around them a few round or polymorphonuclear exudate cells could be seen. The bile capillaries were dilated and contained bile thrombi. The sinusoids in the central areas were in general wide; occasionally the separating connective tissue framework was ruptured. This caused large, centrally located pools of blood. In the peripheral zones the liver cells were intact but separated by edema. Peripherally in the lobules some distorted reconstruction was noted, with beginning formation of pseudolobules. The slightly fibrotic periportal and central fields revealed a few bile-laden exudate cells with few polymorphonuclear leukocytes and little bile duct proliferation.

Comment.—This case of central toxic necrosis appears to be subacute because of periportal and central fibrosis with nodule formation. The blood pools caused by the rupture of the reticulum framework produce a morphologic picture similar to the one described in acute allyl formate intoxication of the dog.[36] Whereas the older literature[37] generally claims that in acute atrophy of the human liver the framework is intact, one occasionally finds a report describing a rupture of the reticulum fibers.[37a] Proliferation of the collapsed reticulum fibers in central necrosis was occasionally seen in this series; it has been described in experimental animals[38] and also in man.[39]

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36. Popper, H.: Ztschr. f. klin. Med. **131**:161, 1937.

37. (*a*) Maresch, R.: Zentralbl. f. allg. Path. u. path. Anat. **16**:641, 1905. (*b*) Kon, J.: Arch. f. Entwcklngsmechn. d. Organ. **26**:492, 1908. (*c*) Huzella, T.: Verhandl. d. deutsch. path. Gesellsch **18**:250, 1921.

38. Popper, H.: Virchows Arch. f. path. Anat. **298**:574, 1937.

39. Herxheimer, G.: Beitr. z. path. Anat. u. z. allg. Path. **43**:84, 1908; **72**:56, 1924.

TIME FACTORS

Conclusions as to the duration of the process and the speed of its progress are possible in some instances. In others, however, the correlation of the clinical and morphologic pictures is rather difficult. This is exemplified by the cases presented now.

Early Acute Toxic Hepatitis (Central Necrosis).—A 51 year old Negro attorney suffered a stroke with resulting hemiplegia four and one-half months prior to his hospitalization. Two days before admission he attempted suicide by swallowing approximately 8 ounces (273 cc.) of an antiseptic, deodorant and disinfectant mixture of coal tar phenols and oils ("creolin"). After administration of starch water he vomited a brownish liquid. At admission his temperature was 101.4 F., and he com-

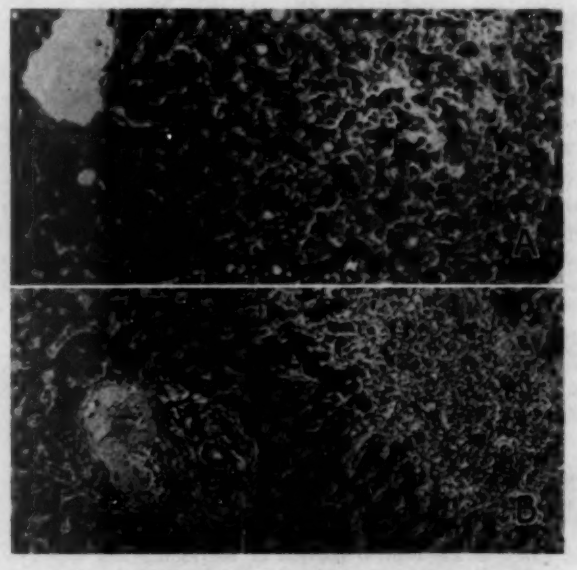

Fig. 10.—*A*, early central toxic necrosis. The arrangement of the liver cell cords of the central zone is distorted. They stain eosinophilic and reveal clumps of coagulated protein. They are surrounded by large numbers of polymorphonuclear leukocytes.

B, late central toxic necrosis. The liver cells in the central half of the lobule have mostly disappeared. In the border zone adjacent to the intact liver cells anuclear cell remnants and fragments are found. There is no fibrosis and little cellular infiltration. The portal triads reveal some polymorphonuclear leukocytes.

plained of severe dysphagia. He exhibited buccal and pharyngeal chemical burns. The scleras were icteric. The urine contained albumin (3 plus) and bilirubin (2 plus). The red cell count was 4,600,000, with hemoglobin 74 per cent; the white cell count was 11,600, with a normal differential count. The Kahn test revealed no syphilis. Despite temporary improvement on dietary and supportive management, he died six days after being admitted to the hospital.

At autopsy the firm liver weighed 1,500 Gm. The surface was smooth and brownish red. On the cut surface the lobular markings were exaggerated, producing a nutmeg appearance. Microscopically (fig. 10 *A*), in the central and intermediate

areas of the lobule the liver cells were shrunken, often dissociated and fragmented. They were eosinophilic and often revealed clumps of coagulated protein and fat droplets of various size in the cytoplasm. The nuclei were preserved. In the wide sinusoids, as well as in the dilated perisinusoidal spaces, many polymorphonuclear leukocytes were found, often surrounding necrotic liver cells. The Kupffer cells were proliferated. Toward the periphery there was noted a gradual transition to normally stained liver cells with only occasional granules of coagulated protein. The periportal fields revealed little infiltration, the cells being chiefly of polymorphonuclear character.

Comment.—In this instance, death due to hepatic insufficiency occurred eight days after the ingestion of the poison. The acute character of the necrosis of the liver cells, which was caused by a chemical substance, is indicated by the fact that the liver cells had not yet been removed and possibly also by the marked leukocytic reaction.

Late Acute Toxic Hepatitis (Central Necrosis).—A 77 year old white man was admitted with epigastric pain of three months' duration. There was progressive decrease in appetite, with loss of 6.5 Kg. (15 pounds) in weight and increasing fatigue on slight exertion. Two weeks before admission progressive jaundice developed. A tender liver was palpable 2 fingerbreadths below the right costal margin. There were moderate anemia and slight leukopenia. The urine contained albumin (1 plus), bilirubin (4 plus) and no urobilinogen. The serum nonprotein nitrogen was 71 mg., the creatinine 2.8 mg. and the total cholesterol 165 mg. per hundred cubic centimeters, with esters 45 per cent. Cephalin-cholesterol flocculation was 4 plus; thymol turbidity, 20.8 units. The stool was free of urobilinogen. Because of suggested extrahepatic biliary obstruction the patient was operated on. However, no changes of the extrahepatic bile ducts were found; the liver was small and softer than normal. His condition deteriorated after the operation. Anuria gradually developed, and the patient died in uremia three weeks after admission.

At autopsy the soft brownish green liver weighed 1,800 Gm. The capsule was smooth and shiny. The edges were sharp. On cut section the lobular structure was made out. The intrahepatic and extrahepatic bile ducts were not dilated. Histologically (fig. 10*B*), in the central portion of the lobules the framework was condensed and denuded, surrounding only a few isolated necrobiotic liver cells and cell fragments. There was hardly any cellular infiltration; there was only some Kupffer cell reaction. Few preserved liver cells revealed clumps of coagulated protein and fatty metamorphosis; in the often narrow peripheral zone only edema was noted. The periportal fields showed some cellular infiltration in which round and polymorphonuclear cells took part. Little, if any, fibrosis was present.

Comment.—The central toxic necrosis and the necrobiotic changes in the surrounding area appeared to be rather recent; nevertheless, the clinical history suggests a far longer duration if the initial clinical symptoms, starting three months before death, can be attributed to hepatic damage. There remains little doubt that the jaundice appearing five weeks before death was caused by the hepatic damage. The long duration of the process is possibly indicated by the fact that the lobules were often small, as shown by the short distance between central vein and portal field. A central necrosis of small diameter may thus be the

result of the disappearance of the greater part of the lobule with subsequent condensation.

In some instances of the viral variety, also, the morphologic picture suggests a duration differing from that indicated by the clinical history.

Subacute Viral Hepatitis with Fulminant Exacerbation.—A 32 year old white soldier had, while in combat overseas, an attack of jaundice associated with vomiting, anorexia and abdominal pain, which was considered infectious hepatitis. He improved quickly in the next few weeks, but when in the following months the jaundice became more marked he was sent back to the United States. On the hospital ship, four days prior to his death, he suddenly became markedly worse. His jaundice increased rapidly, and he became semicomatose and died in cholemia shortly after landing. Two days before death the icterus index was 240; blood urea nitrogen, 8.5 mg. per hundred cubic centimeters; total protein, 7.51 Gm. per hundred cubic centimeters, with a reversed albumin-globulin ratio. The urine showed bilirubin (4 plus) and no urobilinogen. There were slight anemia and leukopenia.

At autopsy the soft and flabby liver weighed 1,150 Gm. Through the smooth capsule, mottled red and yellow areas were seen. On cut section, in wide red depressed areas the lobular pattern was missing; in other yellow-colored areas it was either absent because of nodule formation or was well developed and even exaggerated. The portal triads appeared in general more closely spaced than normal. Microscopically, in part of the liver there was almost complete collapse and denudation of the connective tissue framework. In its meshes one could see mononuclear exudate cells, proliferated Kupffer cells and, chiefly in the periphery, a few proliferating liver cell cords. Liver cell fragments were absent. In other areas the normal structure of the liver cords was preserved. However, not infrequently they were arranged in nodules independent of a central vein. The cords here were distorted, elongated or compressed. Not infrequently, in the centers of the nodules or the lobules a silent denudation of the framework associated with necrobiosis of liver cells, presence of bile-laden large cell fragments and fatty changes were seen. The bile capillaries in this area were markedly dilated and filled with thrombi.

Comment.—The histologic picture is that of a subacute form of viral hepatitis with evidence of some toxic changes probably caused by marked interference with bile and blood flow. The clinical history, however, suggests a disease of low grade and tendency to recovery complicated by a preterminal rapid exacerbation. The latter may possibly be related to the ship's movement, the effect of which can be compared to the described damage resulting from exercise in infectious hepatitis.[4e]

Comparison of the Two Groups.—At present it is difficult to estimate the duration of the disease from the morphologic picture, and further correlation by thorough analysis of individual cases is required. Even the viral form, which seems to run a more uniform course, may occasionally show a severe chronic picture morphologically in instances in which the clinical impression was that of milder disease suddenly complicated by rapid destruction of the parenchyma. The course of the toxic form appears more irregular. Almost identical histologic pictures may be produced in cases in which the duration was only a few days and in those extending over several months.

From a practical clinical point of view these observations emphasize the unpredictability of the outcome of mild forms of primary hepatic necrosis and the necessity of strict therapeutic management.

COMMENT

The selected cases presented may justify a differentiation of two forms of fatal acute primary hepatic necrosis associated with jaundice on a morphologic basis. One is characterized by rapid, almost explosive destruction of the liver cells with only slight centrolobular predominance and marked reaction of the mesenchyma. The other form reveals slow cell death, fatty changes, little mesenchymal reaction and usually marked zonal involvement.

The question of the causation and the nomenclature of these two forms is far more problematic then their morphologic differences. Cases of the first group present a picture rather similar to the one seen in cases of infectious hepatitis in the armed forces and elsewhere.[21] The accepted hypothesis that the recent epidemics of hepatitis are viral in origin suggests a viral causation also for the civilian cases of the first form. This theory is supported by the few instances of this group in which etiologic factors such as administration of blood or plasma were demonstrated. As to cases of the second group, exposure to substances of established hepatotoxic properties was reported in approximately one fifth of the cases, whereas in the remainder no definite etiologic factor could be established from the available, often incomplete, histories. However, the picture simulates that produced in man and animals by known hepatotoxic substances; it also represents a more advanced stage of lesions found in patients with various diseases of well recognized toxic character. Although in the majority of instances no definite causation was demonstrated, the name "toxic" may be applied to the whole group, including the cryptogenic cases. The term "toxic" is considered synonymous with "injurious" or "poisonous" and does not necessarily imply antitoxin-eliciting substances.[28] The possible toxic substances vary in nature and include chemical, pharmaceutic and bacterial poisons (such as those derived from pneumococci or salmonellas) and endogenous injurious substances, as those elaborated in hyperthyroidism. The number of substances reported to be hepatotoxic in man is great.[58] Also, anoxia is to be considered, since passive congestion [31] or disturbances of the hepatic circulation [32] produce a similar picture or at least facilitate its development.[40] That the virus of hepatitis itself may produce similar lesions can obviously not be excluded on the basis of the available material. However, the observation that a "toxic" picture commonly appears in the centers of the nodules or of the lobules in the late stages of viral hepatitis could also be explained

40. Mann, F. C., and Bollman, J. L.: J. A. M. A. **104**:371, 1935.

by circulatory disturbances due to the distorted reconstruction. It therefore would be anoxic and neither an additional toxic factor nor the virus would necessarily have to be considered the cause of these lesions. Further investigations, including transmission experiments, will have to decide whether or not in the later stages of the disease the activity of the necrotizing process is still due to the presence of the virus or is due to a sequela of the original process. The presented observations support the latter hypothesis.

The term "infectious" is better omitted, because certain infectious diseases, such as pneumonia or spirochetal jaundice, may cause a "toxic" appearance. F. B. Mallory spoke of infectious cirrhosis, referring to a Bacterium coli infection ascending through the bile ducts.[41]

The morphologic picture suggests that the probably epitheliotropic virus proliferates in the epithelial cells of the liver. It apparently changes their appearance and staining qualities and interferes with their function. When a certain stage of development of the pathologic process is reached, the liver cells either become hyalinized, owing to diffuse coagulation necrosis (Councilman body) or, more often, disintegrate rapidly (T. B. Mallory [180] speaks of autolysis) into very small fragments, which morphologically are not conspicuous. They are apparently phagocytosed and induce marked mesenchymal reaction. However, even in the subacute form of the disease the death of the individual cell is rapid and still organized larger liver cell fragments are absent. Only in very early examples of the fulminant form can those rapidly disintegrating cells be seen. One may speculate that in milder conditions a few cells disintegrate or hyalinize at one time, whereas in the fulminant, rapidly fatal form, apparently all cells "explode" simultaneously. Draining of phagocytosed material to the lymphatic channels of the portal triads possibly explains the inflammatory, chiefly perilymphatic infiltration in this area. The recovering cells regenerate in a bizarre fashion. A zonal involvement is not always conspicuous; however, the virus may be more effective and the pathologic process of different duration in various parts of the liver, which explains the variegated gross picture.

In contrast, in the toxic form the cell death seems to be slow even in the rapidly disintegrating liver. Regressive changes such as fatty metamorphosis or circumscribed coagulation of cytoplasmatic protein simultaneous with nuclear damage are conspicuous. Consequently, anuclear cell remnants or fragments revealing shadows of cellular structure (ghost cells) are seen. The larger cell fragments seem to induce less inflammation and phagocytosis than the small fragments do in the viral form. That may explain the subdued mesenchymal reaction. Only where complete cells are digested in situ do polymorphonuclear

41. MacMahon, H. E.: Am. J. Path. 7:77, 1931. Mallory.[20]

leukocytes move in, which are in the background in the viral form. Circulatory disturbances, especially in the center of the lobule, seem to be an important part of the picture, and fibrinous thrombi are often seen. The characteristic zonal distribution of the toxic form may in some cases be explained by reduced oxygen tension of the central areas which interferes with destruction and neutralization of some injurious substances. In other instances, which are much less common in this series, the higher concentration of the injurious substances in the peripheral part of the lobule leads to peripheral necrosis without influence of the oxygen tension.[42] The anatomic picture is, in general, well in keeping with an effect of chemical injurious substances interfering with well defined phases of hepatocellular metabolism or with disturbances of circulation, possibly caused by them.[32] As a rule, in this form, a uniform gross picture is seen, since the different lobules are equally and simultaneously involved. It should be emphasized that many changes seen in the toxic form are identical with those seen as results of postmortal autolysis. Further studies are required to determine what is contributed to these changes by premortal, agonal or even postmortal processes.

The cytologic differences between the two groups, especially as to the nature of the death of the cells and their pigmentation, deserve to be clarified further by investigations that can be made only with elaborate histochemical and histophysical methods. On the basis of the material studied so far, in contrast to the Councilman body–like cell, in the ghost cell, characteristic of the toxic form, clumps of coagulation necrosis, if present and even if coalesced to form ramified bodies, are arranged around the nucleus, and the shadow of the structure of the cell is made out. The differences seem to be the same as those between Councilman bodies of yellow fever and hyaline bodies of alcoholic cirrhosis, as pointed out by Ash and Spitz[43]; nevertheless, further investigations would be desirable.

A more intensive study comparing the chronic stages of toxic and viral necrosis appears indicated; however, this could be better carried out in the framework of a study of cirrhosis.

On the presented basis, both lesions, viral and toxic, represent primarily epithelial involvement, with the mesenchymal reaction being apparently an expression of the speed and the character of the epithelial necrosis. From this point of view the term "hepatitis" does not really apply to either of the groups except in the sense of a parenchymatous type of inflammation. It may be still more appropriate to the viral

42. MacCallum, W. G.: A Text-Book of Pathology, ed. 7, Philadelphia, W. B. Saunders Company, 1940.

43. Ash, J. E., and Spitz, S.: Pathology of Tropical Diseases, Philadelphia, W. B. Saunders Company, 1945.

form because of the conspicuous mesenchymal reaction. In most instances of the toxic form, however, the mesenchymal reaction is so limited that the term "fatty degeneration" or "central necrosis" has been usually applied as a morphologic diagnosis.

The nomenclature of the entire group is therefore problematic. The name "hepatosis" has been recommended for conditions with primary epithelial involvement [44] but has not become popular. Noncommittal terms, such as "hepatic necrosis" or "hepatopathy" would be the most correct from the anatomic point of view. Since, however, clinically the term "hepatitis" is applied to these conditions which reveal rather similar clinical and laboratory manifestations, it may in some instances be practical to speak of viral hepatitis and toxic hepatitis instead of hepatic necrosis.

Obviously, only with great hesitation can a morphologic classification of hepatic necrosis be suggested as long as the etiologic factors cannot be demonstrated in individual cases. This classification should, therefore, be considered as tentative and as a working hypothesis which may not cover all cases until more reliable methods of demonstrating viruses and chemical agents are available. The great majority of cases may fall into this classification. Nevertheless, one has to expect some instances which will not follow the presented rule. A few cases were observed which revealed features of both the toxic and the viral group; however, the characteristics of one group predominated. For instance, in a liver showing in general the viral characteristics there may occasionally be found fatty changes and some spotty coagulation necrosis. This can easily be explained by the effect of complicating factors independent of the virus. In addition, the chief difference between the two groups is, in the final analysis, the speed of the necrosis of the liver cells and transitions may occur. Thus it may be possible that in some individual patient a toxin may cause as rapid disintegration of cells as is usually caused by the virus. For instance, cases of toxic hepatitis due to sulfonamides are reported [45] which, according to the description given, would fall into the viral group. In our material the hepatic necrosis following sulfonamide therapy revealed the "toxic" picture.

All our cases in which an etiologic factor was elicited followed the rules outlined. Even established etiologic factors, however, are not easily interpreted; for instance, antisyphilitic administration of arsenical compounds is known to produce hepatic necrosis.[46] It is

44. Roessle, R.: Entzündungen der Leher, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol. 5, pt. 1.

45. Berger, S. S., and Applebaum, H. S.: J. Lab. & Clin. Med. **26**:785, 1941. Herbut, P. A., and Scaricaciottoli, T. M.: Arch. Path. **40**:94, 1945.

46. Wile, V. J., and Sams, W. M.: Am. J. M. Sc. **187**:297, 1934.

now accepted that such treatment may lead to either a toxic form, caused by arsenic, or to the viral form, homologous serum hepatitis, produced when infected blood is transmitted by the syringe during injection of the arsenical preparation. The first form occurs a few days after the injection, whereas the latter may start after several months. Of our 4 patients with a history of arsenical therapy, 2 showed the pattern of viral and 2 that of toxic hepatic necrosis. This explains why the picture of hepatitis following antisyphilitic treatment may be identical with that due to infectious (viral) hepatitis.[47]

The presented interpretations, not the findings, are at variance with the recent, fascinating treaties of Himsworth.[32] What has been called "viral" necrosis in this study corresponds with his massive necrosis. He considers it the result of a delayed effect, chiefly due to malnutrition. What we have called "toxic" necrosis corresponds with his zonal necrosis. Himsworth deserves much credit for pointing out the important role of (sometimes conditioned) malnutrition and of disturbances of circulation. He emphasizes more the extent of the injury and reactions inherent in the liver itself than the etiologic factors in differentiating the two groups. As already stressed, the two forms presented here are not necessarily different etiologic entities. A classification based on morphologic criteria can only suggest causes and cannot be final; it is at best a challenge and stimulus for further discussion.

The incidence of toxic and viral hepatic necrosis may be distorted in the civilian material studied. This material revealed, in contrast with the military material, a striking preponderance of the toxic group. However, before concluding that in the majority of civilian cases fatal primary hepatic necrosis or hepatitis are toxic and not viral in origin, one should keep in mind that in the patients of a large city hospital alcoholism, malnutrition and exposure to hepatotoxic substances may be more prevalent than in the population in general. Moreover, studies based on biopsies performed on the livers of a small number of patients in the same hospital revealed an approximately equal incidence of both forms in cases of benign hepatitis.[48] It appears, therefore, that the toxic form has a relatively higher mortality rate, which may explain the high incidence found at the autopsy table.

The correlation of the clinical and laboratory findings, on one hand, and the morphologic picture, on the other, is still rather hazy. In all cases there was evidence of hepatic failure and jaundice; however, the duration and the severity of the process were not always apparent from the morphologic picture, especially in cases of the toxic form. In some instances in the toxic group death occurred with destruction

47. Dible, J. H., and McMichael, J.: Brit. J. Ven. Dis. **19**:102, 1943.
48. Popper, H., and Franklin, M.: J.A.M.A. **137**:230, 1948.

of a relatively small part of the lobule, whereas in others the entire lobule had disintegrated. The concomitant involvement of other organs, especially of the kidney, with subsequent uremia, may offer a possible explanation for this discrepancy. Further studies of clinicopathologic correlation appear indicated.

A differentiation of the morphologic aspects of the toxic and the viral form of fatal hepatic necrosis is significant, for it may lead to differentiation of two clinical entities. It might be possible to use the morphologic criteria derived from the study of autopsy specimens in the interpretation of biopsy specimens, though with some caution in view of obvious differences between postmortem and biopsy material. Autopsy and biopsy results might be used to differentiate between viral and toxic hepatic necrosis clinically and in the laboratory. Subsequently, the differentiation of toxic and viral hepatic necrosis or hepatitis may emerge from the status of an academic problem into that of prognostic and therapeutic implications.

SUMMARY

The livers of patients dying of acute primary hepatic necrosis with jaundice in the past nineteen years in a large civilian institution (histologic material was available in 95 out of a total of 136 cases) were compared grossly and microscopically with those of a much smaller number of Army personnel. Among 18 of the military specimens 15 revealed various stages of epidemic hepatitis (as described by Lucké [2a]), whereas 3 revealed a different histologic picture. Among 95 civilian specimens 26 showed changes comparable to those in the majority of the livers from Army personnel, whereas 69 revealed central, peripheral or fatty necrosis. The histories elicited from the patients of the latter group indicated that one fifth had been exposed to substances known to be hepatotoxic. The hepatitis of the former group was considered viral in origin, whereas that of the latter was called toxic because it was morphologically similar to the pathologic process observed in man and animals following exposure to substances established as hepatotoxic. Tentative acceptance of two etiologically different groups is suggested, and characteristic morphologic differences are demonstrated, which may be briefly presented as follows:

The "viral" form, which spreads irregularly throughout the liver, reveals sudden death of the liver cells. The cells break up into small fragments or hyalinize diffusely: this process is associated with an energetic mesenchymal reaction involving chiefly mononuclear phagocytosing cells. In the "toxic" form, in contrast, zonal arrangement is more prominent, the death of cells is gradual and large anuclear cell remnants or fragments are visible, which show shadows of cellular structure; the mesenchymal reaction is subdued, and the inflammatory

cells, if present, are often polymorphonuclear; fatty changes are common. The liver is usually larger in the toxic than in the viral form. Renal damage, with azotemia, is more marked in the acute toxic than in the acute viral form.

In chronic phases of the viral form, "toxic" manifestations may appear in the preserved parenchyma, which may be due to anoxia caused by disturbance of the blood flow.

The clinical manifestations of the two forms are briefly referred to, and the difficulty encountered in clinical-pathologic correlation, especially in the "toxic" group, is emphasized. An attempt is made to explain the difference of the morphologic pictures by different mechanisms and speeds of the "viral" and the "toxic" injurious process. Future studies should reveal the incidence of the "toxic" variety in nonfatal cases, since the latter seems to have a higher mortality rate. Although the term "hepatitis" as used for these forms of hepatic necrosis appears unsatisfactory from a pathologic standpoint, it may for the time being be retained because of its widespread clinical use.

HEPATIC HETEROTOPY IN THE SPLENIC CAPSULE

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SUBSEQUENT to finding an accessory liver attached to a human gallbladder, Cullen[1] extensively reviewed hepatic anomalies reported, as far back as 1767. In his opinion anomalies of the liver are infrequent, and, among them isolated nodules of hepatic tissue are "exceedingly rare." Such isolated nodules have been found in the suspensory ligaments of the liver,[1] in Glisson's capsule,[2] in the wall of the gallbladder[3] and scattered over the peritoneum.[2] Insofar as we have been able to determine from the literature[4] compiled subsequent to Cullen's review, there is no report of hepatic heterotopy associated with the spleen.

The following case is not presented as one proved to be an instance of isolated hepatic tissue. Like Gardener,[1] who accidentally discovered hepatic tissue in an adrenal gland, we observed a focus of hepatic tissue in the capsule of a human spleen while examining slides prepared from material obtained at an autopsy.

REPORT OF A CASE

A Negro laborer, aged 59, died suddenly while at work. Death was caused by massive subdural hemorrhage associated with severe cerebral arteriosclerosis. No external or internal congenital abnormalities were noted. The left ventricle of the heart was concentrically hypertrophic. Extensive dense fibrous adhesions were present in both pleural cavities. No adhesions were seen in the abdominal cavity. The viscera, including the liver and the spleen, had been perforated by the embalmer's trochar. The liver weighed 1,850 Gm. Its external and sectioned surfaces showed no pathologic changes.

The spleen weighed 225 Gm. Located centrally on the diaphragmatic surface of the capsule was a slightly roughened irregular gray opaque area, 5 by 4 cm. On sectioning, this area resembled fibrous thickening of the capsule and was sharply demarcated from the subjacent pulp. A few small openings, resem-

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1. Cullen, T. S.: Arch. Surg. **11**:718, 1925.

2. Cited by Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, Philadelphia, W. B. Saunders Company, 1942, p. 741.

3. Thorsness, E. T.: Am. J. Clin. Path. **11**:878, 1941.

4. Quarterly Cumulative Index Medicus, 1925 to June 1946, inclusive.

bling lumens of blood vessels, were seen in the sectioned surface of the thickened area. A small block of tissue was saved for microscopic study.

Microscopic Study of the Spleen.—The peritoneal surface of the thickened area of the capsule was covered by a single layer of mesothelial cells. The mesothelial cells rested in a narrow zone of collagenous connective tissue arranged in coarse bundles. Overlying the splenic pulp was a broader zone of collagenous connective tissue. Between the inner (juxtasplenic) and the outer (juxtamesothelial) zone of connective tissue were groups of well differentiated liver cells, prominent bile ducts, blood vessels and small nerves. These structures were supported by a rather loosely arranged collagenous stroma, which was replacing the liver cells in some regions.

Most of the liver cells were located nearer the juxtamesothelial zone of connective tissue. Although the liver cells were arranged in cords, separated by sinusoids, they did not form the typical lobular pattern. Some sinusoids contained erythrocytes. No bile canaliculi were observed.

Small arteries and veins, each surrounded by a broad collar of connective tissue, were located within and at the borders of the groups of liver cells. No definite correlation existed between these vessels and the hepatic sinusoids.

Most of the bile ducts were conspicuously located between the liver cells and the juxtasplenic zone of connective tissue. The prominent ducts were lined by a single layer of tall columnar cells with basally located nuclei. In one large duct the epithelium formed papillary folds. A conspicuous part of each prominent bile duct was a broad collar of collagenous connective tissue on which the epithelium rested. Intramurally located in some of the "collars" were minute secondary ducts lined by small cuboidal cells. In specially stained sections, elastic tissue was inconspicuous, and muscle fibers were absent from the bile ducts. There was no obvious connection or anatomic lobular relationship between the bile ducts and the liver cells.

The few small nerves present in the supporting stroma resembled sympathetic fibers.

COMMENT

Whether this heterotopic hepatic tissue was attached to the spleen prenatally or postnatally is problematic. However, our sections contained some of the histologic features described by Cameron and Oakley[5] as observed in autoplastic liver transplants in albino rats. After thirty days their transplants contained regions of regenerating liver cells and bile ducts. The liver cells formed prominent sinusoids. Distinctly separated from the liver cells (proved by reconstruction) were bile ducts "ringed around" by concentric layers of collagenous connective tissue. "Budding" of the larger bile ducts was noted. Both bile ducts and liver cells were supported by fibroblasts and coarse collagen.

Regenerating liver cells were not present in our sections of heterotopic liver. Distinct separation of liver cells and bile ducts was observed. The arrangement of the liver cell groups with their sinusoids was similar. "Ringed" and budding bile ducts were present.

5. Cameron, G. R., and Oakley, C. L.: J. Path. & Bact. **38**:17, 1934.

Cameron and Oakley [5] did not observe sympathetic nerve fibers in their sections of autoplastic transplants. In our case the presence of nerve fibers is evidence against a neoplastic origin of the heterotopic liver found in the splenic capsule, for it is generally agreed that the finding of well differentiated sympathetic nerve fibers in a nodule of tissue is evidence against its neoplastic origin (Thorsness [8]).

SUMMARY

A case of hepatic heterotopy involving the splenic capsule is described. Because nerve fibers occurred in the heterotopic liver tissue, it must be assumed that the heterotopic tissue did not constitute a neoplasm and was of antenatal origin.

MEDIONECROSIS OF THE AORTA

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VARIOUS etiologic moments have been held responsible for idiopathic medionecrosis of the aorta since it was first described by Gsell [1] and Erdheim.[2] The work of Erdheim [2] is fundamental and still outstanding. He reviewed the possible etiologic factors and showed preference for some form of hyperadrenalism. He described in great detail the morphologic aspects of the lesion and noted specifically that in those instances in which the typical picture of medial necrosis was shown, vasa vasorum were almost completely absent at the site of rupture. Elsewhere, in the comparatively normal aorta below, these vessels were relatively sparse. In other instances, or where vessels could be found, they showed some degree of hyalinization. Despite this and the later work of Weise,[3] he expressed the belief that the vasa vasorum did not play a role in the production of medionecrosis of the aorta. Later workers [4] also noted alterations of the vasa vasorum.

In routine histologic studies of dissecting aneurysms of the aorta due to so-called idiopathic medionecrosis, we became aware of changes occurring in the vasa vasorum. Thus it was thought of interest to review 12 instances of medionecrosis of the aorta with particular reference to alterations of the vasa vasorum.

MATERIALS

The clinical findings were not contributory. It may be mentioned that the group consisted of 9 men and 3 women, whose ages varied from 26 to 70 years, with an average of 50 years. A history of long-standing hypertension was obtained

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1. Gsell, O.: Virchows Arch. f. path. Anat. **270**:1, 1928.

2. Erdheim, J.: (*a*) Virchows Arch. f. path. Anat. **273**:454, 1929; (*b*) **276**:187, 1930.

3. Weise, W.: Beitr. z. path. Anat. u. z. allg. Path. **93**:238, 1934.

4. Moritz, A. R.: Am. J. Path. **8**:717, 1932. Rottino, A.: Arch. Path. **27**:320, 1939; **28**:1 and 377, 1939. Rottino, A., and Poppiti, R.: ibid. **36**:201, 1943.

from only 1 patient. Some degree of elevation of the diastolic blood pressure with or without systolic elevation was present in 6 others.

Associated postmortem findings were limited to the heart, the aorta and the kidneys.

Cardiac hypertrophy was present in almost every instance. In some it was minimal; in others, pronounced. The cardiac weights varied from 350 to 1,000 Gm. and averaged 522 Gm. The hypertrophy involved principally the left ventricle.

Coronary arteriosclerosis was present in most of these cases. It varied from slight atheromatosis to marked sclerosis and calcifications, with old occlusions. Hemopericardium, due to rupture of the aneurysm, with blood escaping into the pericardial sac, was present in 6.

Valvular changes were found in 3 cases; in 2 these were interpreted as healed endocarditis of the mitral and aortic valves. In the remaining case the mitral and the aortic valve were extremely thick and sclerotic, the latter having only two cusps and being covered with calcific excrescences. In those in which the valvular alterations were interpreted as healed endocarditis there were superimposed bacterial vegetations, acute in one and subacute in the other.

Medionecrosis of the aorta answering to Erdheim's and Gsell's criteria was present in all aortas examined. Two of these in addition had moderate to marked atheromatosis and arteriosclerosis; another, only extensive atheromatosis.

Two of the dissecting aneurysms occurred in aortas with isthmic stenosis. One of the patients was 26 years and the other 29 years old. The heart of the former weighed 530 Gm. and that of the latter 400 Gm.

The kidneys of 3 patients were normal. In those of the remainder, however, changes were present. Arteriolonephrosclerosis was present in the kidneys of 7, 2 of whom also had evidence of chronic pyelonephritis. Interestingly enough, previous unilateral nephrectomies had been performed in 2 instances. Only arteriosclerotic scars were noted in the kidneys of 2 patients. A similar number of patients had hemorrhagic infarctions of the kidneys secondary to lodgment of emboli arising from endocardial vegetations.

METHODS

Whenever possible, numerous blocks of aortic tissue were examined. These were taken not only from the sites of rupture or perforation but from relatively uninvolved zones of the aortas as well. Sections were routinely stained with Delafield's hematoxylin and eosin, and, whenever feasible, with orcein and Masson's trichrome stain.

In an attempt to demonstrate abnormalities in the vascularization of the aorta it was thought that the simplest method would be to inject the vasa vasorum with a radio-opaque material and then subject the aorta to roentgen examination. This procedure had previously been tried with aortas removed from dogs [5a] as well as with normal human aortas. By this means, variations of the vasa vasorum of the aorta have been demonstrated between animals of different species. Additional variations have been noted [5b] among individuals of the same species.

We were able to inject the vasa vasorum in 1 instance of dissecting aneurysm. The injection was performed at the autopsy table before the heart and the aorta were opened. The specimen was then opened by the usual technic, the aorta detached and a roentgenogram made. The distribution of the vasa vasorum is shown in figure 5, compared with that in a normal human control (fig. 4). It is

5. Schlichter, J. G.: (*a*) Am. Heart J. **32**:770, 1946; (*b*) **35**:850, 1948.

apparent that there is no filling of vessels over one particular area at the base. This zone corresponded to the grossly discernible site of tear in the intima and was near the zone of perforation where blood escaped into the pericardial cavity. Microscopically, almost all the vasa vasorum were seen to be filled with the dye. Those which were not were near the site of perforation and had markedly narrowed slitlike or stellate lumens. Narrowing was produced by medial hyperplasia and intimal proliferation. We believe that this method of demonstrating abnormalities in the vasa should be used in every instance of dissecting aneurysm and isthmic stenosis of the aorta.

OBSERVATIONS

Gross Findings.—Dissecting aneurysms were present in every aorta. However, in only 2 aortas could medionecrosis be suspected on gross examination. These revealed pale blue intimal discolorations and puckerings. Their media appeared thin and more translucent than normal.

Microscopic Observations.—Alterations of the aortic media with cystic zones, fulfilling all the established criteria for idiopathic cystic necrosis, were found in all 12 aortas. However, of most interest were the changes in the vasa vasorum.

Alterations were encountered in the vasa vasorum of 7 of the 12 aortas. They varied in type and severity. Changes were present in small and larger vessels of the adventitia. Whatever the morphologic picture, marked narrowing of the lumen seemed to be the end result. Some smaller arteries, as well as arterioles, showed principally marked hypertrophy of the media (figs. 1 and 2). Others, in addition, were narrowed by profound splitting and reduplication of the internal elastic membranes with or without subintimal deposition of lipids and hyaline substance (figs. 1 and 3). In several, the splitting of the internal elastic membrane was accompanied by clumping and distortion of the fibers, so that a continuous membrane no longer existed. Lumens were frequently reduced to narrow transverse or stellate slits. Narrowing of the smallest arterioles was frequently accomplished through hyperplasia or swelling of endothelial cells, in addition to medial hypertrophy. In 2 aortas vasa vasorum were rarely seen. When they could be found, they showed profound alterations in their media and intima. In another aorta, in addition to medial hypertrophy and intimal hyperplasia, several smaller arteries in the adventitia were involved by a collagenous type of degeneration involving all coats but not accompanied by an inflammatory reaction.

Inflammatory cells were found in the adventitia of 7 of the 12 aortas. The exudate varied from small accumulations of lymphocytes and plasma cells, some perivascular, to extensive and rather dense aggregates of lymphocytes, polymorphonuclear leukocytes, macrophages and fibroblasts. Several apparently were the results of slow dissection with the formation of granulation tissue (fig. 1).

In regard to 2 aortas with narrowings of the vasa vasorum, the possibility of rheumatic arteritis was considered, in one instance because of typical associated endocardial changes, and in the other because of the abundance of large histiocytes, some multinucleated, about the vasa vasorum.

Since many patients with dissecting aneurysm have vascular hypertension, a recent study of the aortas of 40 patients with hypertension [6] is of interest. Twenty-three of the 40 aortas showed changes in the adventitia with frequent accumulations of lymphocytes. In 35 per cent, however, there was hypertrophy of the media of the vasa vasorum and occasional luminal narrowings due to subendothelial depositions of hyaline substance. For the most part these findings are in accord with ours.

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6. Ashworth, C. T., and Haynes, D. M.: Am. J. Path. **24**:195, 1948.

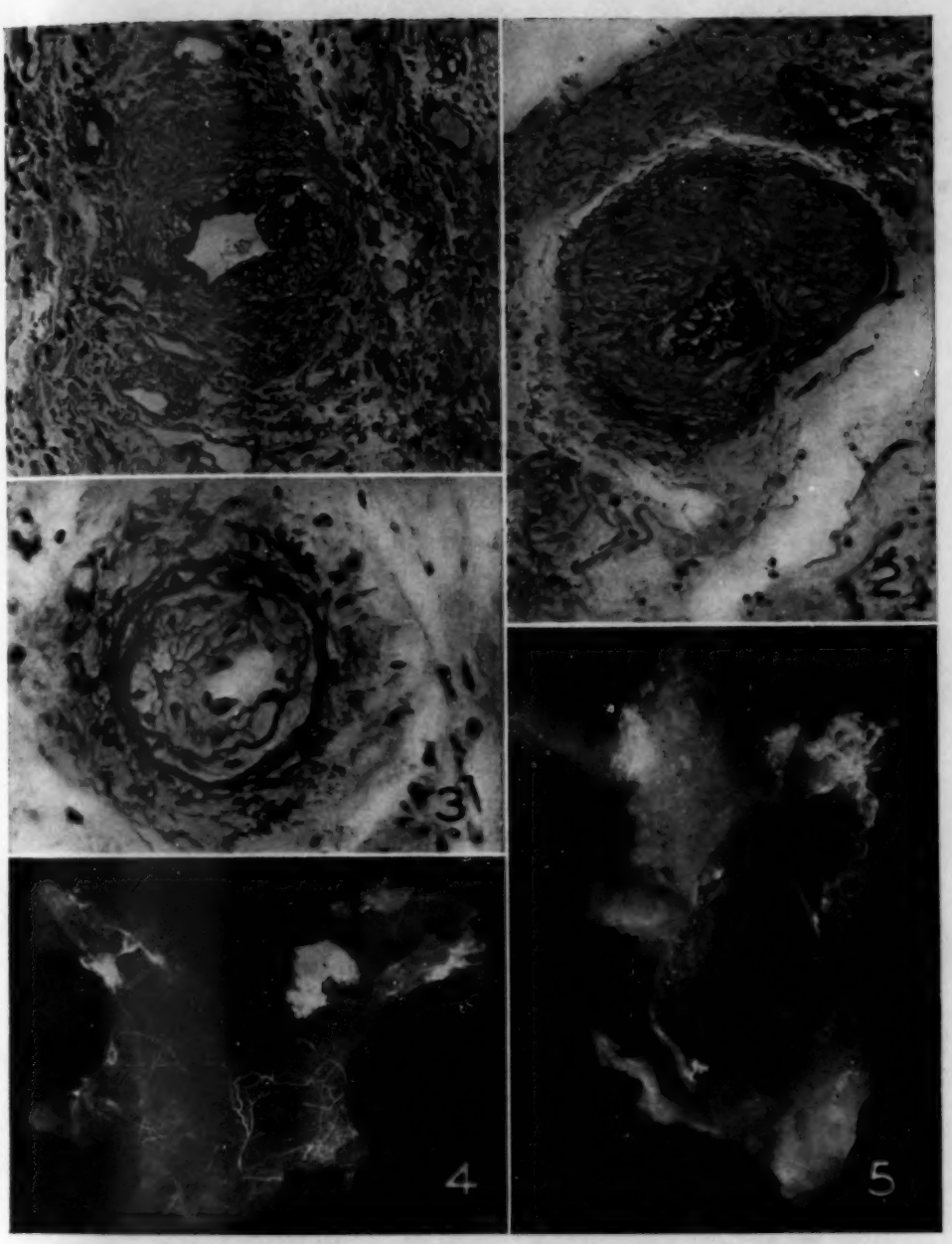

Fig. 1.—Hypertrophy of the media and reduplication of the internal elastic membrane of a small artery surrounded by granulation tissue. Orcein and iron-hematoxylin stain; × 130.

Fig. 2.—Marked hypertrophy of the media and reduplication of the internal elastic membrane, with almost complete obliteration of the lumen, of a small artery. Orcein and iron-hematoxylin stain; × 130.

Fig. 3.—Profound luminal narrowing caused by endothelial proliferation and reduplication of the internal elastic membrane of a small artery. Orcein and iron-hematoxylin stain; × 279.

Fig. 4.—Roentgenogram of the vasa vasorum at the root of a normal human aorta, which were injected with radiopaque material. The aortic cusps are at the bottom of the illustration.

Fig. 5.—Roentgenogram of the vasa vasorum of the root and arch of the aorta in a patient with a dissecting aneurysm. Note the lack of filling of the vasa vasorum a short distance above the cusps. This zone corresponded to the site of rupture of the dissecting aneurysm and the most severe histologic alterations of the vasa vasorum.

For purposes of comparison we examined the ascending aortas from 20 patients who were normotensive and whose ages averaged 53 years. Hyalinization of the media of the vasa vasorum without luminal narrowings was encountered in 5 patients aged 61, 61, 66, 72 and 76 years, respectively. In the aortas of 3 other patients, aged 50, 66 and 73 years, respectively, narrowings of the lumens of the vasa vasorum in addition to medial or intimal hyperplasia were found. Luminal narrowings of a group of small arteries of the vasa vasorum of the 73 year old patient were at the immediate site of a large arteriosclerotic plaque which impinged on and disrupted the inner third of the media of the aorta. With exclusion of this patient, only 2 of the 20 routine controls had narrowings of the vasa vasorum without medial or pronounced intimal changes in the aorta. These alterations were less pronounced and extensive as compared with those of the group with dissecting aneurysms.

COMMENT

We encountered pathologic changes in the vasa vasorum of 7 of our patients with dissecting aneurysm. They varied from slight to pronounced arteriolosclerosis and arteriosclerosis with hypertrophy or hyperplasia of media and intima. In all, luminal narrowings were present. Abnormalities of the distribution and of the filling of the vascular bed were demonstrated in 1 aorta at autopsy by injecting the vasa vasorum with a radiopaque material. It is conceivable that the alterations of the vasa vasorum alone may result in anoxia of the aortic media.

Hypertension of vessels seems important in several respects. It may be the cause of hyperplastic intimal changes of small arteries in some instances. These changes may be the immediate or an important contributory cause of medionecrosis. After the medionecrosis has been established, even in persons whose blood vessels are normotensive, a transitory hypertension such as that produced by physical or emotional stress may increase the spread of the dissection as well as increase the chance of rupture.

As a result of ischemia of portions of the aorta, the media undergoes infarctions, or necrosis. This may manifest itself as zones of loss of structure and gradual accumulations of loose connective tissue. Some of these lesions may heal as described by Erdheim; others may become the seat of continued dissection, with hemorrhage due to tearing of blood vessels of the aortic media. "Zones of ischemia" of the aorta are suggested by those authors who believe that dissecting aneurysms may result from rupture of the vasa vasorum. Such a mechanism, i. e., vasospasm with necrosis of the distal portion of the vessel, may play a role in some patients with hypertension but without histologic alterations in the vasa vasorum.

Medionecrosis of the aorta or of peripheral vessels has been produced experimentally by chemical or mechanical means that interfere with the vascularization as carried out through the vasa vasorum of the adven-

titia in rabbits and, more recently, in dogs.[7] The importance of the nutrition of the aorta which is carried on by way of the vasa vasorum was demonstrated by one of us, by means of coagulation of the adventitia of the ascending aorta, in dogs.[7]

As one reviews our cases and the voluminous literature on dissecting aneurysm of the aorta, it becomes apparent that this disease is not an entity in itself but is the result of varying physiologic and morphologic alterations of the wall of the aorta. The pathologic picture varies with the etiologic factor. All cases, however, have one feature in common, i. e., the destruction of the aortic media. The aorta so damaged may yield to the normal or to the increased intra-aortic pressure with spontaneous rupture or with the formation of a dissecting aneurysm and rupture.

In view of the accumulated experimental and morphologic evidence it may be suggested that the factor responsible for idiopathic cystic necrosis of the aorta is ischemia of the media. This can be produced by pathologic changes of the vasa vasorum resulting in narrowing of their lumens. Such alterations may be due to a localized variety of arteriolosclerosis or arteriosclerosis and may or may not be associated with similar changes occurring elsewhere, particularly in the kidneys.

SUMMARY

Twelve dissecting aneurysms of the aorta associated with "idiopathic" medionecrosis were studied. Narrowings of the lumens were found in the vasa vasorum of 7. Ischemia of the media of the aorta was implicated as the underlying primary factor in the production of medionecrosis.

7. Schlichter, J. G.: Arch. Path. 42:182, 1946.

MAMMARY LIPOMA

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IN AN extensive series of cases of tumor of the breast, critically analyzed, Haagensen [1] found that a number of conditions considered clinically to be cancerous were shown by histologic examination to be various changes of fat tissue. In one of these cases the breast had been unnecessarily removed. Commenting on this unfortunate occurrence, Haagensen recalled a similar case reported by Keynes,[2] in which a xanthomatous degeneration observed in the frozen sections was mistaken for carcinoma and a radical mastectomy performed. The frequency of mistaken diagnosis is still more apparent in Menville's [3] series, necrosis of fat having been mistaken for cancer in 20 per cent of the cases and xanthomatous degeneration in an additional 11 per cent. These few but significant figures call for new endeavor in the understanding of the pathologic involvements of the fatty framework of the breast. One primary liposarcoma and 11 new growths of fat tissue found among 274 consecutive mammary tumors removed at operation are presented here. The variety of patterns exhibited by the new growths seemed worthy of comment and an attempt at orderly classification of the growths.

HISTORICAL REVIEW

Fatty tumors of the breast are rare and have interested few writers. The first specimen properly recorded is that now in the Gordon Museum of Guy's Hospital and referred to by Holmes and Hulke [4] in their "System of Surgery." It consisted of "several pounds of fat which had been growing in the site of the mammary gland for 58 years." The patient died in 1860, at the age of 87 years, having been troubled only by the bulk of the pendulous tumor, which measured 23 inches (58.5 cm.) in circumference. This tumor is representative

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1. Haagensen, C. D.: Am. J. Cancer **16**:1077, 1932.
2. Keynes, cited by Haagensen.[1]
3. Menville, J. G.: Am. J. Cancer **24**:797, 1935.
4. Holmes, T., and Hulke, J. W.: A System of Surgery, London, Smith, Elder & Co., 1883.

of the usually slow growth of fatty tumors of the breast, but rapid growth of one of these tumors is occasionally noted.

Adair, Pack and Farrior [5] reported 134 cases of lipoma, in 15 of which the tumor occurred in the breast in a location which made clinical diagnosis difficult. In most of these cases it was retromammary, difficult to palpate and, owing to its elasticity, it often simulated the consistency of a deep cyst. When localized in the mammary fold it caused dimpling where it was attached to the skin, similar to that seen in the case of a sweat gland carcinoma. When in the axilla, it could not always be differentiated from aberrant breast tissue or from cyst of a large apocrine sweat gland.

Among the 622 cases of lipid tumor reviewed by Geschickter [6] there were 39 in which the breast was involved, in 3 by liposarcoma and in 36 by lipoma. In 5 of the 39 cases, either both breasts were affected, or multiple fatty nodules were present in the same breast—a multiplicity of lesions that obviously might lead to a false impression of cystic disease.

Among the 58 cases of conditions affecting the fatty framework of the breast reported by Menville there were 9 cases of xanthomatous growth, 25 cases of fat necrosis and 24 cases of lipoma. Pain was present in 6.5 per cent of the cases and retraction of skin in 4.4 per cent—data which emphasize the necessity of microscopic study of biopsy material.

There were 27 cases of lipoma (in 1 of which the patient was a male) in de Cholnoky's [7] series. These comprised 3.7 per cent of all cases of simple tumor of the mammary gland and 1 per cent of all pathologic conditions of the breast. These figures correspond closely with the 2 per cent of lipid tumors of the breast reported by Kleinschmidt.[8]

That fatty tumors of the breast are uncommon enough to warrant description even of individual specimens is shown by the recent reports of Spalding [9] and Halpert and Young.[10] Spalding recognized among his 3 cases two different types, one consisting of fatty tissue only and the other of a combination of fatty tissue and glandular epithelium, which were growing together in a coordinate fashion to form a well differentiated adenolipoma. This subdivision was not accepted by Halpert and Young. Any new growth of fat tissue, either localized or diffuse, centering around the epithelial structures of the mammary

5. Adair, F. E.; Pack, G. T., and Farrior, J. H.: Am. J. Cancer **16**:1104, 1932.
6. Geschickter, C. F.: Am. J. Cancer **21**:617, 1934.
7. de Cholnoky, T.: Arch. Surg. **38**:79, 1939.
8. Kleinschmidt, O.: Chirurg **3**:297, 1931.
9. Spalding, J. E.: Guy's Hosp. Rep. **24-25**:80, 1945-1946.
10. Halpert, B., and Young, M. O.: Arch. Path. **42**:641, 1946.

glands, they ascribed to lipomatosis. The term "mammary lipoma" they reserved for the growths characterized by a focal aggregation of well differentiated fat cells delimited by a capsule and located within the mammary gland proper.

MATERIAL AND CLINICAL DATA

Among the 274 conditions of the breast requiring surgical intervention at the Framingham Union Hospital during the last ten years, twelve were classified as fat tissue new growths, one of which was a liposarcoma. Thus 4.6 per cent were lipid growths, including simple and cancerous forms, a figure which is slightly higher than that reported by de Cholnoky [7] and Kleinschmidt.[8] Simple fat tissue growths made up 5.5 per cent of conditions not requiring mastectomy. The only liposarcoma represented 1.5 per cent of all cancers, which included sixty-three carcinomas and one fibrosarcoma.

Of the 12 fatty tumors of this series, 11 were in females and 1 in a male, a distribution already shown by de Cholnoky [7] and by Holland.[11] The greatest incidence was in the fourth and fifth decades of life, but all age groups were represented, the youngest patient being a woman of 25 and the eldest a woman of 75. None of these tumors were found to have occurred before the age of puberty. In 4 instances the marital status was not mentioned; 2 of the patients were single, and all others had one or more children. Three of the patients were obese and the others of normal habitus.

Only in 2 cases was there a possible relation between the fatty new growth and previous trauma. One case was that of a 49 year old woman whose breast was struck twice, the first time eighteen months and the second time six months prior to the development of the mammary tumor, which occurred at the site of the trauma. In this as in other similar reported cases it was not possible to establish a causative relation between the trauma and the tumor. In the other case, that of a 61 year old woman, a lipoma developed beneath the scar resulting from a radical mastectomy performed for cancer four years before. The fatty mass was excised and found to be noncapsulated. The growth slowly recurred, and three years later the newly formed mass was removed; microscopically, its structure was unchanged.

In 9 of the 12 cases of fatty tumor of the breast the fat tissue growth represented the only pathologic condition that had been seen in the breast. A case in which a previous cancer had been removed has already been mentioned; in another case a fibroadenoma had been removed some time before from the opposite breast, and in a third a fibroadenoma had been excised from the same breast four months before the fatty tumor made its appearance. New growths elsewhere in the body included a cervical polyp in one case and multiple uterine leiomyoma in another.

In none of the cases of simple lipoma was the tumor fixed to the skin or to deeper structures. There was no retraction of the nipple, duplication, local redness or increased heat or palpable axillary lymph nodes. Localized tenderness was present in 10 cases. In 2 cases the preoperative diagnosis was fibroadenoma and in 8 cases cystic mastitis.

The apparent duration of the simple tumors varied from three weeks to five years. Even considering the fact that a tumor may remain unnoticed for a long period, only in 3 instances did one gain the impression that the tumor had rapidly

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11. Holland, T. E.: Canad. M. A. J. **32**:74, 1935.

increased in size; in the majority of cases the growth of the tumor was slow, with long periods in which it was stationary. In the case of the liposarcoma the patient asked for medical advice one month after she had first noticed the "lump."

LOCALIZATION AND GROSS CHARACTERISTICS

In 5 cases the site of the growth was the right breast; in 7, the left, including the 2 instances with multiplicity of growths. The upper outer quadrant appeared to be the most frequent site (8 cases), followed in order by the upper inner quadrant (3 cases), the fold (1 case) and the areolar edge (1 case). In 1 instance the tumor was retromammary, a localization that is generally considered commoner than the intraglandular one. The patient was a 43 year old woman. The growth, the size of a small cherry at the time it was noticed five years previously, grew slowly, reaching the size of a grapefruit at the time of removal. Roentgenograms of the breast showed an encapsulated mass of uniform density which displaced and compressed the glandular tissue to a thin crescent. A faint shadow suggested that the pectoral muscles overlay the tumor. At operation the tumor was found to be a well encapsulated lipoma, 17 by 13 by 10 cm., located underneath the pectoralis major muscle.

Multiplicity of growth was observed in the breast in 2 cases. In one case a tumor was located at the fold close to the axilla and another in the upper outer quadrant. In the other case two tumors were embedded in the upper outer quadrant.

What was interpreted as a recurrence occurred in a single instance, that of a 61 year old woman previously submitted to mastectomy for carcinoma. Whether this case should be considered among those of mammary lipoma is questionable as it might find better classification among those of subcutaneous lipoma of the mammary region.

The cases of fatty new growth included many varieties of form, size and distribution. In some the tumor was nodular and encapsulated, and in others diffuse deposits involved areas ranging from 1 cm. in diameter to virtually the entire breast. In 8 cases the tumor was encapsulated, and in 6 it was not encapsulated. In one of the 2 cases with multiplicity of growth the breast contained two masses, both of which were nodular and encapsulated. In the other case the breast also contained two masses, both occurring as diffuse fatty deposits. The size ranged from 1.2 to 17 cm. in diameter. The size of the tumor usually varied with its duration, but no definite relation could be found between existence and size.

The gross examination usually showed these tumors to be lobulated, pale yellow or golden yellow, and soft in consistency. Fibrous septums were evident both externally and on the cut section. The size of

the lobules and the thickness of the interlacing fibrous bands varied. Differences in color and in the size of the lobules were often distinct as these growths were compared with the normal surrounding fat.

MICROSCOPIC PATTERNS

As for the intimate structure, the fourteen lipid tumors of this series were classified as follows:

Mature and Well Differentiated Fat Tissue (5 cases).—This was the most frequent pattern in this series. The proliferated fat tissue was the same as normal fat tissue and failed to show increase in cellularity pointing to active potentiality of growth (fig. 1). Tumors of this type would be expected to give a history of slow growth. However, the structure of the most rapidly growing tumor of this series was of this type. Sections taken from many areas of the tumor failed to show foci of cellularity which could account for the rapid growth.

Mature Fat Tissue with Foci of Cellularity (2 cases).—A number of authors have ventured the opinion that recurrences of supposedly simple fatty lipomas are due to the presence of immature cells missed through incomplete histologic study. It is common experience, however, that entirely mature cell growths, arousing no suspicion of potential cancer from the histologic standpoint, may later be the site of repeated recurrences. It is also well known that fatty growths containing immature mesenchymal cells giving a false impression of progressive potentialities of growth frequently fail to recur. This fact suggests that multicentric foci of cellularity represent the actual matrix of new fat cells which, unless accompanied by demonstrable cellular anaplasia and evidence of abnormal mitoses, does not indicate cancer. The 2 tumors of this series in which multicentric foci of cellularity were found were both rather small, one encapsulated. Neither has recurred, one and three years, respectively, after removal.

The cells making up the foci included elements of lymphocytoid character (interpreted as histiocytes) and cells of a larger type, resembling a plasma cell which, as pointed out elsewhere,[12] possibly represents the forerunner of the larger foam cell (fig. 2). The intimate admixture, in these foci, of fibroblasts, histiocytes and lipid cells in various stages of development again raises the question of the genetic relationship of these different cell types.

Figure 3 illustrates a close arrangement of lipoblasts. Whether or not the adipose cells are capable of multiplying once they have

12. Tedeschi, C. G.: Experimental Embryonal Cell Sarcoma, Arch. Path., to be published.

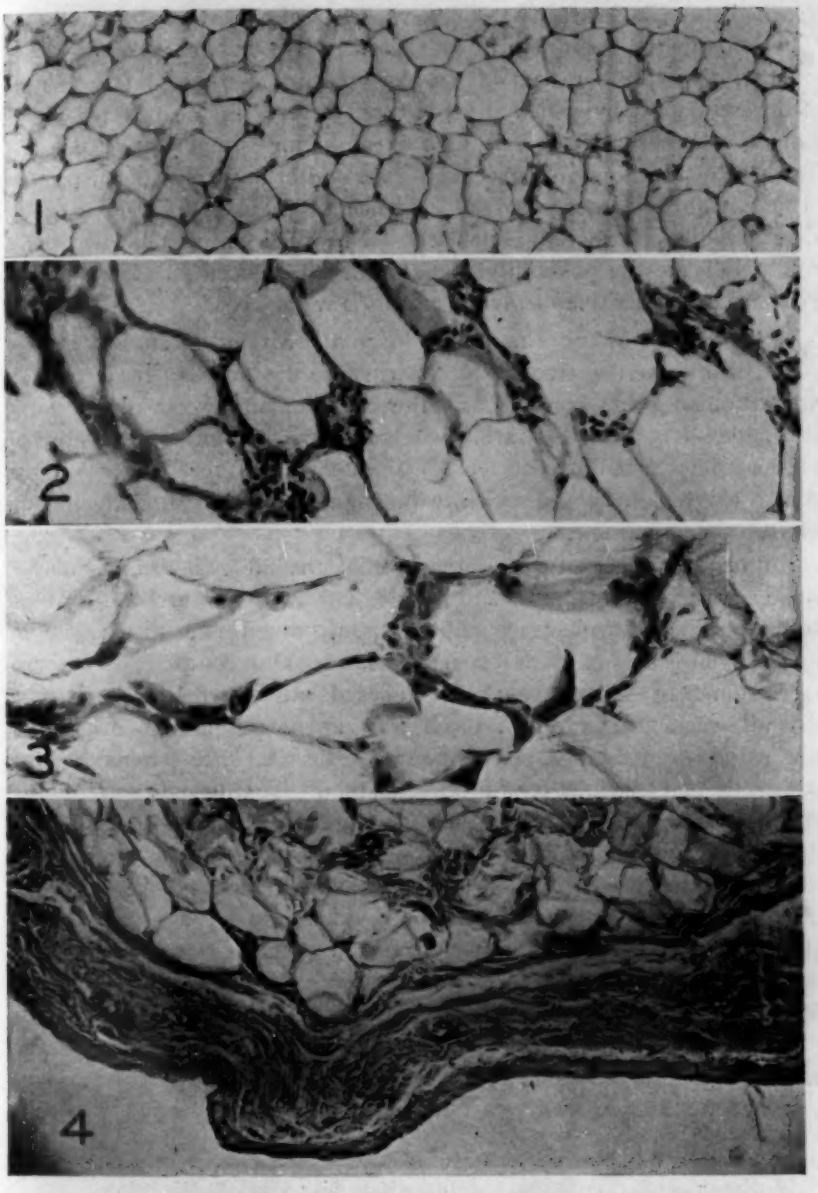

Fig. 1.—Mature, well differentiated lipoma of retromammary localization, growing to the size of a large grapefruit in a five year period. Zeiss lens, ocular 5, objective 10.

Fig. 2.—Encapsulated, slow growing lipoma (2 cm. in diameter) showing foci of cellularity, most numerous at the capsular boundary. No recurrence after three years. Zeiss lens, ocular 10, objective 10.

Fig. 3.—Foci of lipocytic proliferation in a diffuse and well differentiated lipomatous growth. Zeiss lens, ocular 5, objective 40.

Fig. 4.—Collagen formation and marginal sclerosis in a capsulated, mature lipoma. Zeiss lens, ocular 7, objective 10.

reached their full maturity (Kölliker [13]) is still a matter of controversy. This possibility was denied by Wassermann,[14] who expressed the opinion that proliferation of fat cells occurs through a process of dedifferentiation by which the adult cell reverts to the original pluripotent reticulum cell that is capable of giving rise to new fat cells. In the absence of any other cellular type and of any transitional pattern which might be interpreted as evidence of cellular differentiation or dedifferentiation, foci of lipoblastic cells such as that shown here might indicate the possibility that the mature fat cell is, under certain circumstances, capable of giving rise to new fat cells.

Involutional Changes in Well Differentiated Fat Tissue (2 cases). —According to the traditional description, the adipose tissue of the adult human being consists of large cells containing fat in the form of single globules which are encircled by a thin envelope of protoplasm. The presiding nucleus, dislocated from the center of the cell to the periphery, gives rise to the signet ring cell, so characteristic of this type of tissue.

A new conception of the structure of the fat cell was introduced some years ago by Marchand [15] and Policard.[16] Marchand, in his study on the transplant of adipose tissue, noted that the cuticle of the fat cell was not of a plasmatic nature and compared it to the sarcolemma of striated muscle. Policard attempted to demonstrate that the membrane of the fat cell was not of ectoplasmic origin but was made up of the collagenous fibers of the fat tissue stroma, against which the fat globule lay directly, without the interposition of any other structure. The fat particles floating in the blood stream would therefore enter the cell by a simple physical process conditioned to the colloidal status of the cell. It is now generally accepted (Schaffer [17]) that the wall of the fat cell can be divided into a thin inner protoplasmatic layer enclosing the nucleus at one point of the circumference, and an outer membrane of reticular fibers, the thickness of which depends on the amount of pressure that may be exerted on the cells. Favilli [18] and Volterra [19] have given excellent illustrations of the interlacing of argentaffin fibers enveloping the fat cell. According to Nageotte and Guyon,[20] a thick network of interlacing precolla-

13. Kölliker, A.: Anat. Anz. **1**:206, 1886.

14. Kassermann, F.: Ztschr. f. Zellforsch. u. mikr. Anat. **3**:235, 1926.

15. Marchand, F.: Beitr. z. path. Anat. u. z. allg. Path. **61**:1, 1920.

16. Policard, A.: Compt. rend. Soc. de biol. **87**:944, 1922.

17. Schaffer, J., in von Möllendorf, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1930, p. 74.

18. Favilli, G.: Sperimentale, Arch. di biol. **87**:629, 1928.

19. Volterra, M.: Sperimentale, Arch. di biol. **81**:319, 1927.

20. Nageotte, J., and Guyon, L.: Compt. rend. Soc. de biol. **88**:1288, 1923.

genous fibers, branching and anastomosing on one another, gives rise to a trabeculated structure, in the meshes of which lie the fat cell, "like a balloon suspended in its net."

Under normal circumstances this meshwork cannot be seen unless special stains are applied. It becomes apparent, however, on the formation of collagen in the argentaffin reticulum, an occurrence the significance of which has been little investigated. Thickening of the mesenchymal involucre of the fat cell of a mild degree was seen rather frequently in the fatty new growths of this series. In 2 cases, however, the degree of sclerosis was so striking that a word of comment cannot be amiss. In one case, as represented in figure 4, the process was most apparent at the periphery of the growth (marginal sclerosis), while in the other the process was present throughout the fatty nodule (fig. 5). I would interpret this productive fibrosis as an involutional phenomenon.

Mature Fat Tissue and Glandular Tissue (3 cases).—It has been emphasized many times that the periductal fibrous tissue of the breast must be considered as an intrinsic part of the secretory apparatus. It responds with the glandular structures to ovarian stimulation, and it shares with them practically all the dysplastic mammary states. The intralobular connective tissue which surrounds the secreting elements is, in general, much more cellular than the interlobular connective tissue and contains practically no fat. Since juxtaposition of mammary epithelium and fat does not occur in the breast, as a rule, the combination of epithelial structures and fat tissue in 3 of our cases is unusual. In 2 cases the new growth was nodular and encapsulated and consisted of fatty tissue in which epithelial ducts were sparsely scattered. The fat cells were predominant and lay in direct contact with the ducts (fig. 6). The epithelium lining the ducts was low cuboidal or distorted by reciprocal compression and filled the lumens almost completely. No glandular acini could be recognized in either one of the two new growths. The patterns in these two tumors compare exactly with Spalding's [9] description of a tumor classified as adenolipoma. He assumed that the tumor had arisen within the mammary lobule by proliferation of the epithelial and connective tissue cells, the latter differentiating into fat cells instead of the usual connective tissue cells. This possibility cannot be denied, but it is more logical to interpret the combination as the result of the revival of embryonal mammary elements segregated into the breast during development. The following points favor this view: (*a*) the presence of a capsular boundary, (*b*) the absence of glandular acini and (*c*), most important, the direct juxtaposition of mammary epi-

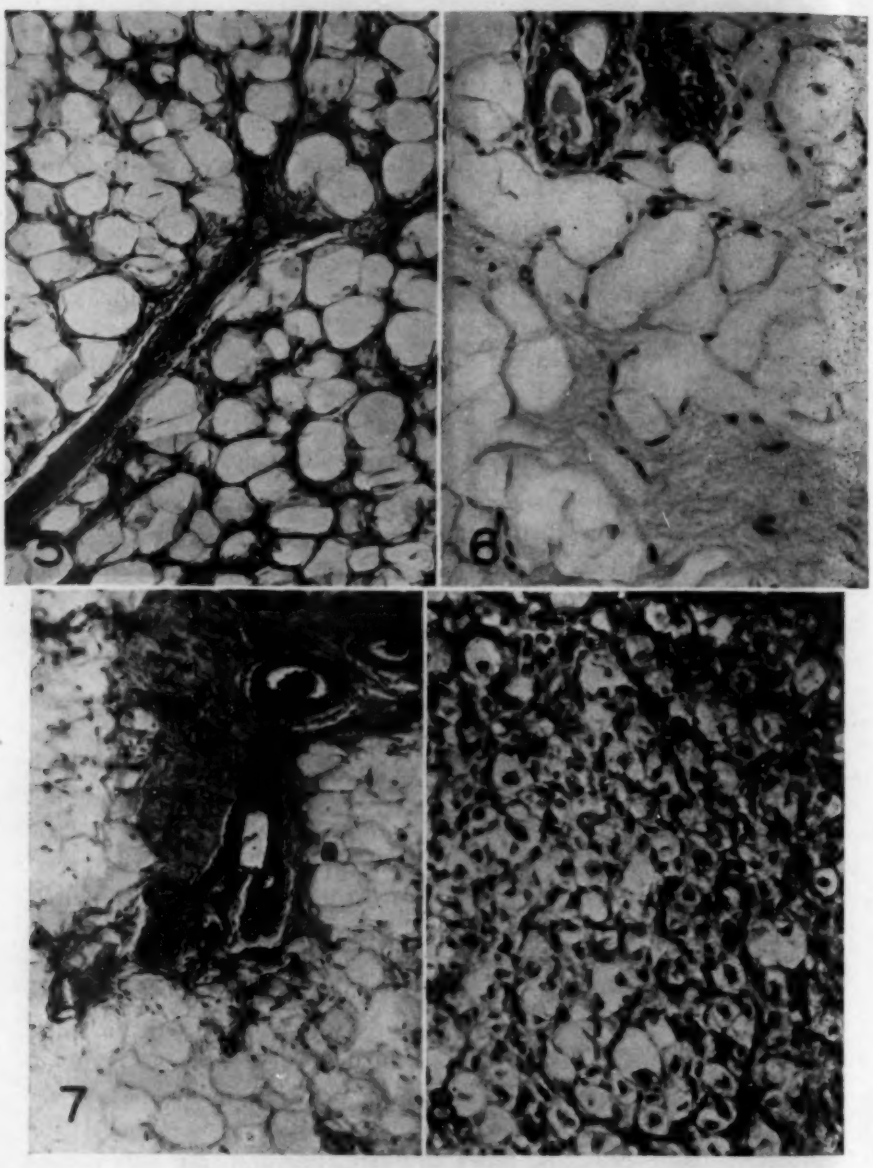

Fig. 5.—Thickening of the argentaffin reticulum and collagen formation in a diffuse lipomatous growth. Zeiss lens, ocular 7, objective 10.

Fig. 6.—Fatty cells lying in direct contact with epithelial ducts. True adenolipoma. Zeiss lens, ocular 10, objective 10.

Fig. 7.—Overgrown fat tissue infiltrating and displacing the tissue proper of the breast and giving rise to an adenolipomatous pattern. Zeiss lens, ocular 7, objective 10.

Fig. 8.—Liposarcoma, mature cell type. Zeiss lens, ocular 5, objective 4.

thelium and fat, a condition which seems to be found normally only in the embryonal breast (Hamilton, Boyd and Mossman [21]).

Spalding's interpretation might apply, however, to the third case of this group, in which the tumor was characterized by the presence of fat and glandular elements. In this case, however, the new growth was not encapsulated, and between the duct walls and the fat tissue there was a thick layer of connective tissue stroma which was more dense and less cellular than the normal intralobular connective tissue (fig. 7). Glandular acini were also recognizable, and since the epithelial structures were not evenly distributed the resulting pattern may have been brought about by overgrown fat tissue infiltrating and displacing the tissue proper of the breast rather than by intralobular connective tissue cells differentiating into fat tissue cells.

Mature Fat Tissue and Fibrous Connective Tissue (1 case).—This combination was found in but 1 case. The tumor was a small encapsulated nodule; the outer aspect was fatty, whereas the central area was composed of firm, pale gray and glistening tissue from which thin bands radiated in various directions. Except for the capsule, the gross appearance was similar to that of a scirrhous carcinoma. Microscopically, both fat and fibrous tissue were well differentiated, and there were no cellular patterns pointing to a transitional developmental stage. The neoplastic combination of the two tissues might be interpreted as an expression of the multiple developmental potentialities of the undifferentiated mesenchymal cell of the fat lobule.

Liposarcoma (1 case).—Embryologically lipoblasts are found in either of the following forms: Cells which are round or polyhedral and since early development have been grouped together in gland-like lobules of a moruloid structure; or widely spaced stellate or spindle-shaped cells which gradually become rounded and assume characteristics of fat cells as droplets of lipoid material accumulate within their cytoplasm and which are embedded in a highly vascularized mucoid mesenchyma. These two embryologic forms are reproduced with great exactness by the cancerous lipoblastic tumors. Those which reproduce the embryonal mesenchymal tissue are generally myxomatous and include a fibrosarcomatous tissue mixed with lipoblasts. The other shows rounded or polygonal lipoblasts of varying sizes and an admixture of mature fat cells and of fat-laden phagocytes without any myxomatous or fibroblastic tissue.

The latter was the pattern shown by the only cancerous lipoblastic tumor included in this series. The patient was a 75 year old woman who had first noticed the mass one month previously. At the time

21. Hamilton, J. J.; Boyd, J. D., and Mossman, H. W.: Human Embryology, Baltimore, Williams & Wilkins Company, 1945.

of operation the tumor was 6 cm. in diameter. Almost all the axillary lymph nodes showed metastatic involvement which exactly reproduced the cellular and structural characteristics of the primary tumor.

In this case the differential diagnosis centers primarily on the xanthoma group. According to Haagensen's [1] classification, xanthoma falls into one or the other of the following two main categories: (*a*) primary xanthoma (xanthosarcoma of the English and Germans, *xanthom en tumeurs* of the French), which is interpreted as a local manifestation of the syndrome of xanthomatosis; (*b*) secondary xanthoma (or better, pseudoxanthoma, Aschoff [22]), a retrogressive change likely to occur in any inflammatory or neoplastic tissue. The fundamental distinction between the two groups is made on histologic structure. Primary xanthoma is made wholly of xanthoma cells and can occur in any part of the body, including the breast.[23] Pseudoxanthoma contains not only xanthoma cells but also inflammatory cells if arising or growing in inflammatory tissue or among tumor cells. The absence of any other type of neoplastic structure or of a primary inflammatory process rules out in my case xanthomatous degeneration occurring in inflammatory or neoplastic tissue. As for primary xanthoma, the cells of the tumor with their round or polyhedral shape, round nucleus and lightly stained foamy cytoplasm closely simulated xanthoma cells under the lower power of the microscope, but they were larger than the usual xanthoma cells, mature fat cells were present in abundance and no doubly refractive crystals of cholesterol esters could be recognized, either free or intracellular (fig. 8).

SUMMARY AND CONCLUSIONS

The simplest way to classify the fatty tumors of the breast region on topographic and gross criteria seems to be to divide them into four broad groups on the basis of whether the tumor is provided with a capsule or is free from any capsular boundary, or whether it has arisen in the fatty framework of the breast itself (intramammary lipoma) or in the retromammary or the subcutaneous fat and has clinically involved the breast (paramammary lipoma).

As for the microscopic structure, the first main subdivision must be traced between the growths consisting of fatty tissue only and those in which other tissues are present in the tumor.

In the group of the pure fatty growths, the mature and well differentiated type, the sclerosing or involutional type and the one provided with multicentric foci of cellularity deserve recognition not

22. Aschoff, L.: Pathologische Anatomie, Jena, Gustav Fischer, 1923, p. 997.

23. Cheatle, G. L., and Cutler, M.: Tumors of the Breast, Philadelphia, J. B. Lippincott Company, 1932, p. 307. Haagensen.[1]

only for their distinct structural pattern but for the justified expectancy of a different potentiality of growth, that is to say, for the prospect of a different clinical outcome.

In the group of the fatty tumors in which other tissues enter into the composition, a combination of fatty tissue and of fibrous connective tissue, on one hand, and of fatty tissue and of epithelial glandular elements, on the other, exemplify the two types of homologous and heterologous mixed fatty tumor.

The homologous type is interpreted as an expression of the multiple developmental potentialities of the undifferentiated mesenchymal cell of the fat lobule.

Since juxtaposition of mammary epithelium and fat does not, as a rule, occur in the mature breast but can be found in the embryonal breast, a revival of embryonal mammary elements segregated into the breast tissue during development is the hypothesis proposed to explain the coordinate proliferation of fat tissue and of glandular elements. This suggestion, of course, does not rule out the possibility that a mixed fatty and glandular tumor may have resulted because intralobular connective tissue cells differentiated into fat tissue cells. In both eventualities the ensuing pattern is that of true adenolipoma. This label obviously does not apply to tumors in which a combination of glandular elements and fatty tissue has been brought about because the tissue proper of the breast was infiltrated and displaced by overgrown fat tissue, as illustrated in one of my cases.

The subdivision generally accepted for liposarcoma, namely an embryonal type and a mature cell type, stands also for the cancerous growths arising in the fatty framework of the breast. The only cancerous lipoblastic tumor included in this series exemplified the mature cell type.

ABSENCE OF RENAL LESIONS IN RATS RECEIVING A SYNTHETIC DIET LOW IN PROTEIN

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IN AN interesting physiologic and pathologic study of rats receiving a low protein, natural diet with either carrots or turnips as the primary constituent, Dicker, Heller and Hewer [1] observed histologic renal lesions of some degree in 67 of 84 rats, or 80 per cent. The lesion consisted of calcified renal tubular casts with a surrounding foreign body reaction, similar to those seen in chronic alkalosis [2] and in dietary chloride deficiency producing chronic alkalosis.[3] For this reason it seems of interest to determine whether low protein intake itself produces this renal lesion or whether some other property of the natural diet is to be considered responsible.

METHODS

The following diet was employed: casein 1 per cent, sucrose 75 per cent, vegetable oil 17 per cent, salt mixture 4 per cent, cod liver oil 2 per cent and wheat germ oil 1 per cent. To each kilogram of diet the following supplements were added: thiamine hydrochloride, inositol and para-aminobenzoic acid, 160 mg. of each; calcium pantothenate, riboflavin and pyridoxine, 80 mg. of each; nicotinc acid 500 mg. and choline chloride 2.0 Gm. Male rate were used, 5 varying in weight from 325 to 360 Gm. and 5 from 140 to 180 Gm. The animals were maintained on this diet until each had lost approximately one third of its original body weight, a decline requiring approximately eight weeks in the first group and five weeks in the second. At this time rats were killed and tissues fixed for histologic examination.

RESULTS

None of the rats showed the renal tubular obstructive lesion described previously.[1] One of the larger rats showed extreme fatty infiltration of the liver with early cirrhosis of the type described by György and Goldblatt [4] and by Webster.[5]

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1. Dicker, S. E.; Heller, H., and Hewer, T. F.: Brit. J. Exper. Path. **27**:158, 1946.
2. Cooke, A. M.: Quart. J. Med. **2**:539, 1933.
3. Lowenhaupt, E., and Greenberg, D. M.: Arch. Path. **42**:49, 1946.
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COMMENT

The duration of the experiment and the loss of weight on this synthetic diet are approximately equal to those on the natural diet.[1] Although the protein of the latter diet cannot be accurately computed, that of the former produces a similar biologic response. The absence of renal tubular lesions would suggest that lack of protein alone is not the responsible factor.

The original authors [1] excluded choline deficiency and high serine dietary content as responsible agents, mentioning the similar lesions produced in uric acid and in phosphate nephritis. However, they failed to consider the possible contribution of the high content of carrot or of turnip (85 per cent). Of all usual vegetables,[6] both carrots and turnips are among those that are highest in residual alkaline elements: carrots with 14 cc., turnips with 12 cc. and potatoes next with 9 cc. of normal alkali per hundred grams. Both carrots and turnips are high in calcium and in phosphates.[6] Thus it seems quite likely that this diet might produce a chronically alkaline urine containing large quantities of calcium and phosphates. This is the ideal condition for the precipitation of calcium phosphate casts in the ascending loops of Henle and in the distal convoluted tubules as discussed in the case of chloride deficiency of the rat.[3] This is likewise observed in chronic alkalosis,[2] and, just as in both of those conditions, the lesion consists first in the presence of precipitated calcium with a consequent surrounding foreign body reaction. Inability to acidify the urine might be increased by the physiologic damage of low protein.[1]

The low incidence of hepatic lesions is to be explained by the acuteness and the short duration of the deficiency in contrast to the longer survival on a diet higher in protein.[4]

SUMMARY

It is concluded that low protein intake is not responsible for the renal tubular lesion occurring in rats fed a low protein, carrot and turnip diet. Chronically alkaline urine containing large amounts of calcium and phosphates is suggested as the basis for the precipitation of calcium in the tubules, with a foreign body reaction occurring about the cast. An identical lesion is described in chronic alkalosis and is produced in the rat by a chloride-deficient diet.

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6. Bowes, A. deP., and Church, C. F.: Food Values of Portions Commonly Used, ed. 6, Philadelphia, Anna de Plantar Bowes, 1946. Sherman, H. C., and Lanford, C. S.: Essentials of Nutrition, New York, The Macmillan Company, 1940.

Books Received

BRONCHIOGENIC CARCINOMA AND ADENOMA. WITH A CHAPTER ON MEDIASTINAL TUMORS. By B. M. Fried, M.D., associate attending physician of Montefiore Hospital for Chronic Diseases, New York. Pp. 306, with 118 illustrations. Price $6. Baltimore: Williams & Wilkins Company, 1948.

This book consists of 306 pages and considers the subject of bronchogenic carcinoma in all its aspects. Much space (106 pages) is devoted to incidence, pathologic anatomy, etiologic factors and metastases. These features are presented in a commendable manner, and this part of the book seems a good source for reference purposes.

The chapters devoted to clinical manifestations and diagnosis present the material well and bring out the most recent developments. The more important features of the condition are stressed, and much clinical material is used to emphasize the various aspects of the disease.

The chapter on treatment is quite inadequate and at times misleading. There is a general tendency to overemphasize the value of roentgen therapy. Much of the reference material used in the discussion of surgical management of the lesion is old and outdated. Few of the advances described in recent publications are mentioned. Thus, there is ground for real criticism of an otherwise well prepared book concerning this most important problem.

The chapter on adenoma is satisfying for such a controversial subject. The chapter on mediastinal lesions is sketchy. In the opinion of the reviewer this material would better have been omitted except as a subject for discussion in the differential diagnosis of primary tumors of the lung.

HISTOPATHOLOGY OF THE PERIPHERAL AND CENTRAL NERVOUS SYSTEMS. By George B. Hassin, M.D., emeritus professor of neurology at the University of Illinois College of Medicine, Chicago. Third edition (revised and enlarged). Pp. 612, with 325 illustrations. Price $8.50. Privately printed, 1948.

The first edition appeared in 1933, the second in 1940. The present edition includes the most recent advances in its field. Chapters on catabolic diseases, trauma of the cauda equina and the histology of spina bifida are added; also new illustrations; and the bibliographies and the index are enlarged. There are five parts: general considerations, diseases of peripheral nerves and muscles, diseases of the spinal cord, diseases of the brain, staining methods. The illustrations, all black and white, are well done. Hassin's book continues to be a good guide to the study of the microscopic morphology of diseases of the nervous system.